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Targan et al.

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(54) **METHODS OF IDENTIFYING THE GENETIC BASIS OF A DISEASE BY A COMBINATORIAL GENOMICS APPROACH, BIOLOGICAL PATHWAY APPROACH, AND SEQUENTIAL APPROACH**

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Related U.S. Application Data

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(51) **Int. Cl.**
G01N 33/48 (2006.01)
G06F 19/00 (2011.01)

(52) **U.S. Cl.**
CPC ***G06F 19/34*** (2013.01)

(58) **Field of Classification Search**
CPC G06F 19/34
USPC 702/19
See application file for complete search history.

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(57) **ABSTRACT**

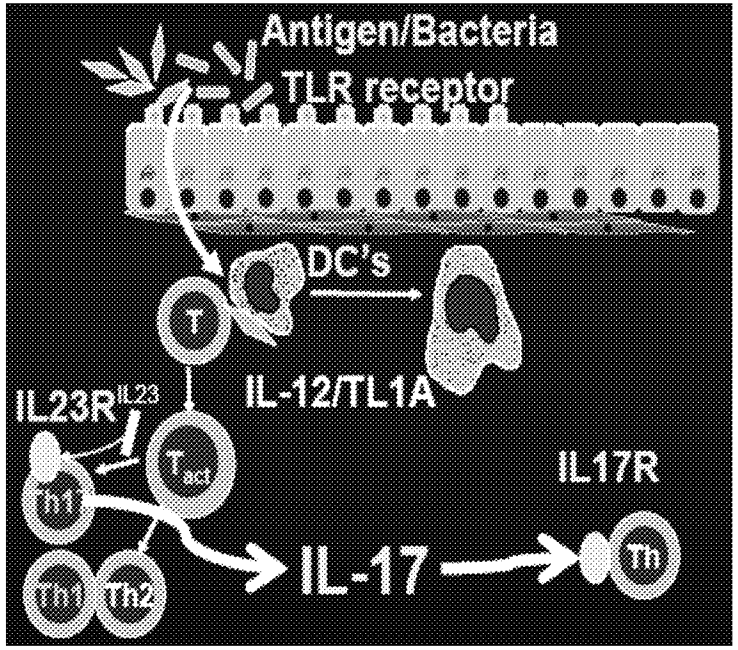
In one embodiment, the invention provides methods of identifying genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease. In another embodiment, the disease is stratified by use of an immune response to disease-associated antigens. In another embodiment, the invention provides methods of identifying pathways that, either alone or in combination, are important to the pathogenesis of a disease. In another embodiment, the invention provides a method of diagnosing or predicting susceptibility to a disease in an individual by determining the presence or absence of genes and genetic variants that, either alone or in combination, are important to the pathogenesis of the disease.

8 Claims, 41 Drawing Sheets

FIG. 1

(PRIOR ART)

(a)



(b)

IL23R & IL17 (p for interaction = 0.047)		
IL23R risk	IL17 risk	OR
No	No	1.0
No	Yes	1.0
Yes	No	1.1
Yes	Yes	2.4
IL23R & IL17R (p for interaction = 0.036)		
IL23R risk	IL17R risk	OR
No	No	1.0
No	Yes	1.1
Yes	No	1.3
Yes	Yes	3.0

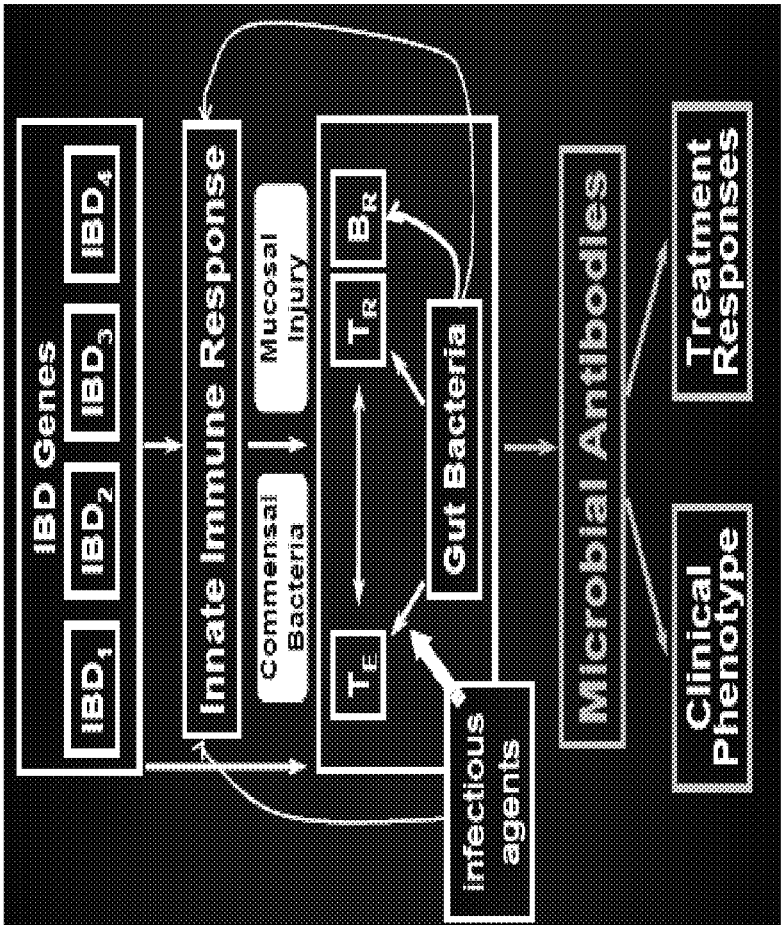


FIG. 2
(PRIOR ART)

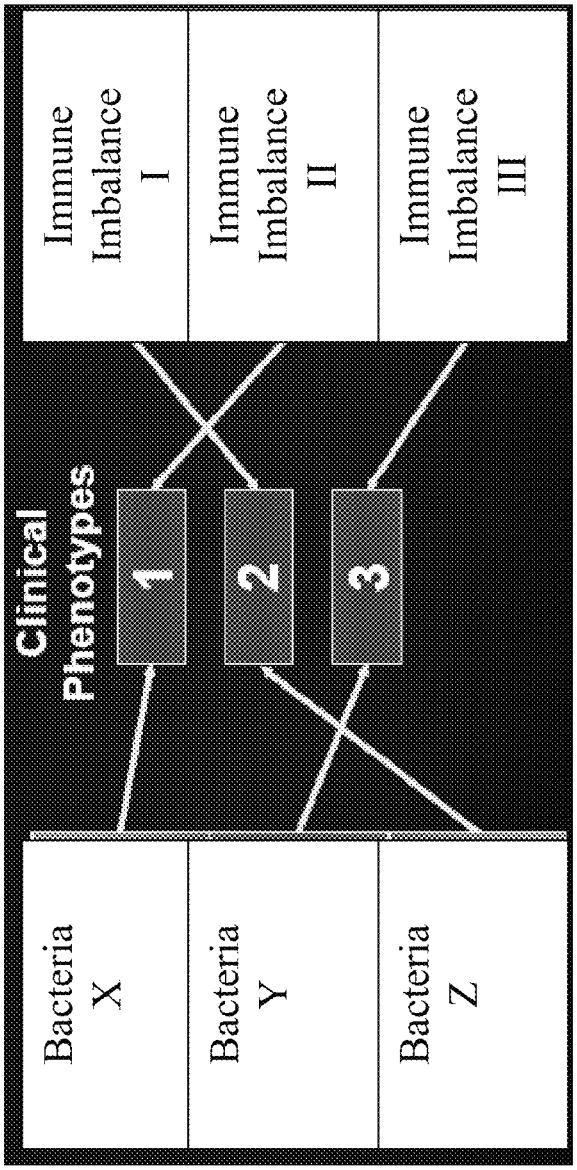


FIG. 3
(PRIOR ART)

FIG. 4

(PRIOR ART)

Organism	Antigen	Name
Saccharomyces	Oligosaccharide	ASCA
Commensal bacteria	Neutrophil nucleus	pANCA
E. Coli	Outer Membrane Porin C	Anti-OMPC
Pseudomonas fluorescens	I-2 sequence	Anti I2
Clostridium sp.	Flagellin	Anti-CBir

FIG. 5

(PRIOR ART)

	SB	Fibrosten.	Int. Perf.	SB Surg.	UC-like
Anti-I2	-	P=0.027	-	P<0.03	-
Anti-OmpC	-	-	P<0.02	-	-
ASCA	P=0.003	P=0.0001	P=0.0008	P=0.0007	P=0.0002
NOD2	P<0.03	-	-	-	P<0.05
Anti-Cbir1	P=O.018	P=0.05	P=0.008	-	-

FIG. 6

(PRIOR ART)

ASCA	Anti-CBir1
Permeability/adherins PTPRB	Myeloid activity PTPRG (IFNγ)
Endosomal transport EHD3	TCR activation TCRα, PTPRC, MGAT5
Innate channel KCNMA1 (CGD mimic)	Transactivation IκBAP "NFκB", Fib, RA17
TCR co-activation BTNL2, PAK7	Endothelial response ZF124
Cell activation RAC/CDC42 SRGAP3	

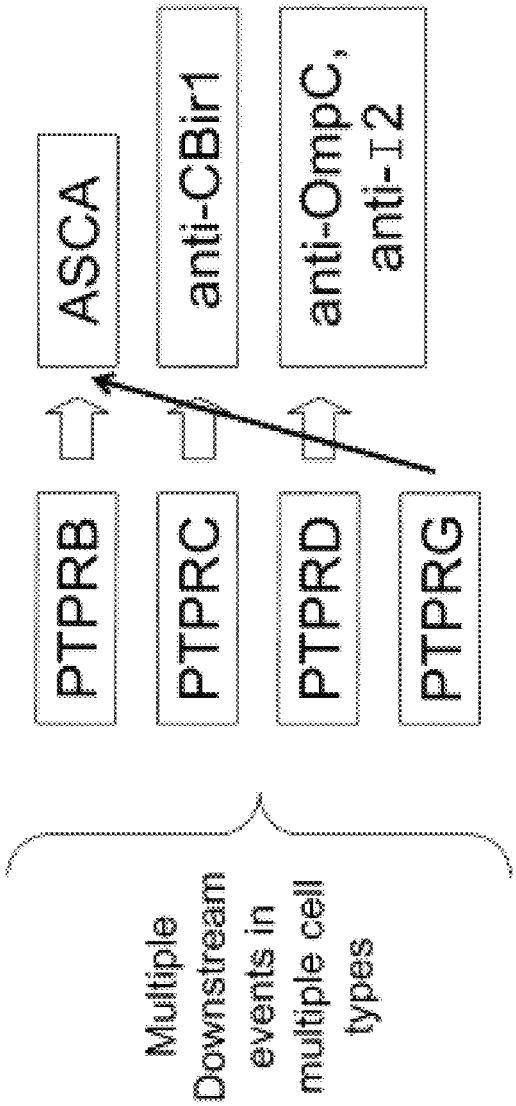


FIG. 7
(PRIOR ART)

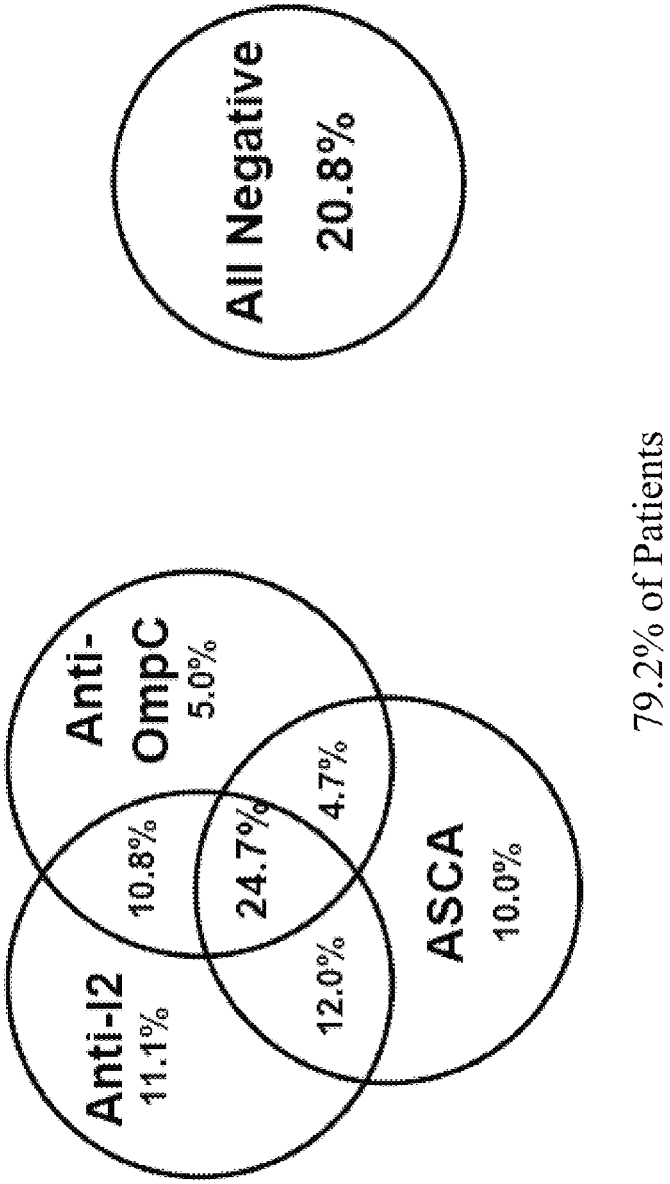


FIG. 8
(PRIOR ART)

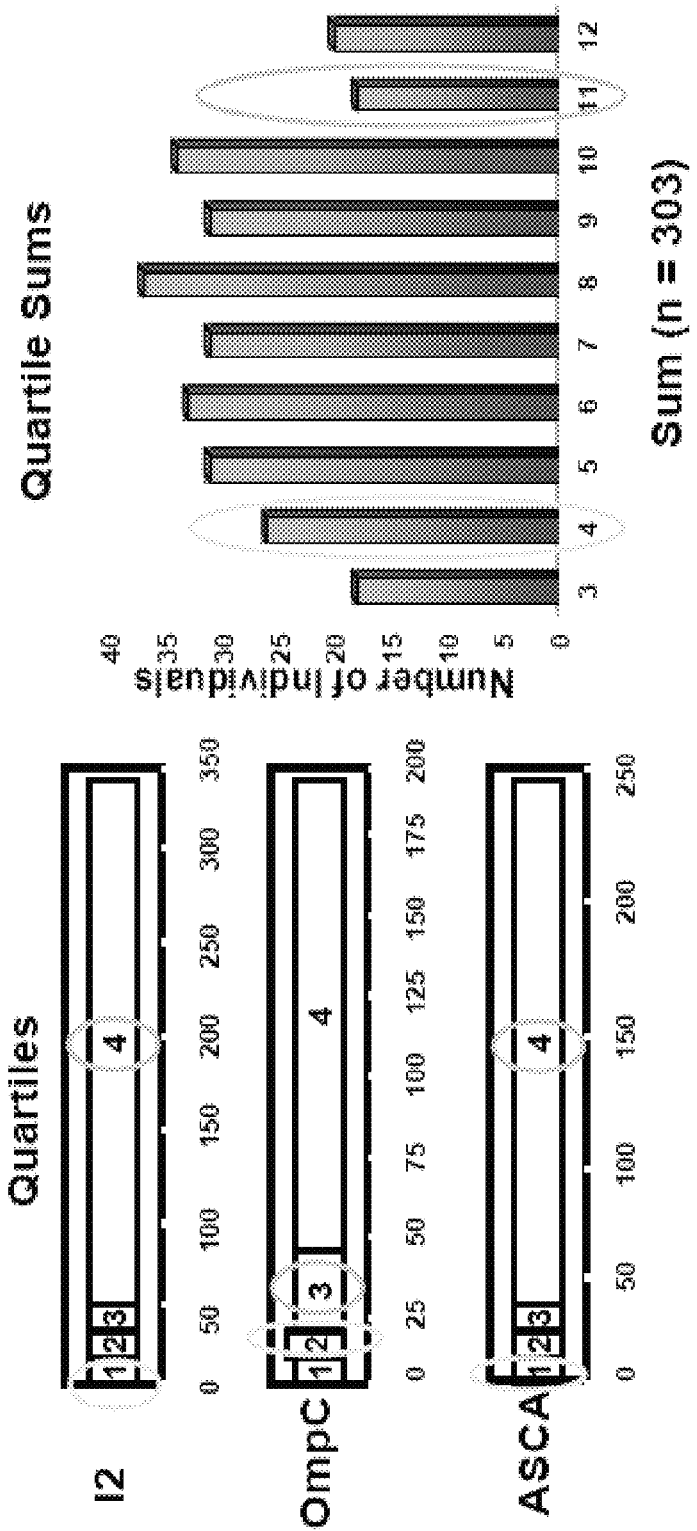


FIG. 9
(PRIOR ART)

FIG. 10A

CHR	position.dbsnp126	SNP	Import-ance	p-value by permutation	ANTI-BODY	MEASURE-MENT	TRANS-FORM.	gene.id	genes	gene::description
1	10737525	rs205483	XXXXX	0.000001	anti-I2	PRESENCE ABSENCE		54897	CASZ1	castor zinc finger 1
1	10737525	rs205483	xxx	0.00005848	ALL	SUM	QUARTILE	54897	CASZ1	castor zinc finger 1
1	18449300	rs223198	xxx	0.00004237	IgG	LEVEL		84966	IGSF21	immunoglobin superfamily, member 21
1	18449300	rs223198	xxx	0.00004932	IgG	LEVEL	LOGARITHMIC	84966	IGSF21	immunoglobin superfamily, member 21
1	111828556	rs1361133	xxx	0.00005289	anti-OMPC	PRESENCE ABSENCE		140	ADORA3	adenosine A3 receptor
1	215319172	rs1553347	xxx	0.000018	ASCA	PRESENCE ABSENCE		2104	ESRRG	estrogen-related receptor gamma
1	215319172	rs1553347	XXXXX	0.000001	IgA	PRESENCE ABSENCE		2104	ESRRG	estrogen-related receptor gamma
1	215319172	rs1553347	xxx	0.000026	IgA	LEVEL	LOGARITHMIC	2104	ESRRG	estrogen-related receptor gamma
1	230576628	rs3120767	xxx	0.00006873	anti-I2	PRESENCE ABSENCE		57568	SIPA1L2	signal-induced proliferation-associated 1 like 2
1	230580289	rs789358	XXXXX	0.000002	anti-I2	PRESENCE ABSENCE		57568	SIPA1L2	signal-induced proliferation-associated 1 like 2
2	10374017	rs6709696	xxx	0.00005155	anti-OMPC	PRESENCE ABSENCE		3241	HPCAL1	hippocalcin-like 1
2	66174003	rs7597203	xxx	0.00004957	ASCA	PRESENCE ABSENCE		440867	FLJ16124	FLJ16124 protein
2	70027133	rs10496176	XXXXX	0.000008	IgG	LEVEL		4084	MXD1	MAX dimerization protein 1
2	70027133	rs10496176	xxx	0.00009543	IgG	LEVEL	LOGARITHMIC	4084	MXD1	MAX dimerization protein 1

FIG. 10B

2	79794682	rs6725030	xxx	0.00005753	IgA	LEVEL	LOGARITHMIC	1496	CTNNA2	catenin (cadherin-associated protein), alpha 2
2	101709494	rs6543092	xxx	0.00006515	ASCA	PRESENCE ABSENCE		9448	MAP4K4	mitogen-activated protein kinase kinase kinase kinase 4
2	101769603	rs4616501	xxx	0.00008511	ASCA	PRESENCE ABSENCE		9448	MAP4K4	mitogen-activated protein kinase kinase kinase kinase 4
2	202209693	rs1208081	xxx	0.00008761	ALL	SUM	ADJUSTED	65062	ALS2CR4	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 4
2	223457806	rs705727	xxx	0.00007843	ALL	SUM	ADJUSTED	2181	ACSL3	acyl-CoA synthetase long-chain family member 3
2	223457806	rs705727	xxx	0.00007477	ALL	SUM	QUARTILE	2181	ACSL3	acyl-CoA synthetase long-chain family member 3
3	4722360	rs13313995	xxx	0.000032	anti-CBir1	PRESENCE ABSENCE		3708	ITPR1	inositol 1,4,5-triphosphate receptor, type 1
3	10421826	rs2160871	xxx	0.00007648	IgG	LEVEL		491	ATP2B2	ATPase, Ca++ transporting, plasma membrane 2
3	41433642	rs9872216	xxx	0.00004723	IgG	LEVEL		54986	ULK4	unc-51-like kinase 4 (C. elegans)
3	54956017	rs1878110	xxx	0.00004556	anti-CBir1	PRESENCE ABSENCE		55799	CACNA2D3	calcium channel, voltage-dependent, alpha 2/delta 3 subunit
3	98889288	rs13318801	xxx	0.00005618	IgG	LEVEL		285220	EPHA6	EPH receptor A6
3	121077178	rs3108749	xxx	0.000017	IgG	LEVEL	LOGARITHMIC	2932	GSK3B	glycogen synthase kinase 3 beta
3	121078193	rs1719895	xxx	0.000017	IgG	LEVEL	LOGARITHMIC	2932	GSK3B	glycogen synthase kinase 3 beta

FIG. 10C

3	157721229	rs4254605	xxx	0.0000796	anti-CBir1	PRESENCE ABSENCE		7881	KCNAB1	potassium voltage-gated channel, shaker-related subfamily, beta member 1
3	159311016	rs11713363	xxx	0.00004057	anti-I2	PRESENCE ABSENCE		51319	RSRC1	arginine/serine-rich coiled-coil 1
3	159311016	rs11713363	xxx	0.00004608	ALL	SUM	QUARTILE	51319	RSRC1	arginine/serine-rich coiled-coil 1
3	159490501	rs1210359	xxx	0.00009592	anti-I2	PRESENCE ABSENCE		51319	RSRC1	arginine/serine-rich coiled-coil 1
3	186392827	rs11919970	xxx	0.000016	anti-I2	PRESENCE ABSENCE		1962	EHHADH	enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase
3	193394497	rs12488465	xxx	0.00007612	IgG	PRESENCE ABSENCE		2257	FGF12	fibroblast growth factor 12
3	195562211	rs13070515	xxx	0.00009256	ASCA	PRESENCE ABSENCE		131578	LRRC15	leucine rich repeat containing 15
4	4321627	rs7671899	xxx	0.000012	anti-I2	LEVEL		55646	LYAR	hypothetical protein FLJ20425
4	5503796	rs7678335	xxx	0.00007812	IgG	LEVEL		55351	STK32B	serine/threonine kinase 32B
4	5503796	rs7678335	xxx	0.00008048	IgG	LEVEL	LOGARITHMIC	55351	STK32B	serine/threonine kinase 32B
4	5513915	rs1034748	xxx	0.00006468	IgG	LEVEL	LOGARITHMIC	55351	STK32B	serine/threonine kinase 32B
4	16094104	rs872182	XXXXX	0.000006	ALL	SUM	ADJUSTED	9079	LDB2	LIM domain binding 2
4	16094104	rs872182	xxx	0.000026	ALL	SUM	QUARTILE	9079	LDB2	LIM domain binding 2
4	46701156	rs13139021	XXXXX	0.000004	anti-CBir1	PRESENCE ABSENCE		2557	GABRA4	gamma-aminobutyric acid (GABA) A receptor, alpha 4

FIG. 10D

4	74936965	rs872914	xxx	0.00007484	IgA	PRESENCE ABSENCE		5197	PF4V1	platelet factor 4 variant 1
4	82103746	rs1052325	xxx	0.00005731	IgA	LEVEL		255119	C4orf22	chromosome 4 open reading frame 22
4	96612588	rs265060	xxx	0.00009921	IgA	LEVEL		8633	UNC5C	unc-5 homolog C (C. elegans)
4	96612588	rs265060	xxx	0.00008529	ALL	SUM	ADJUSTED	8633	UNC5C	unc-5 homolog C (C. elegans)
4	96612588	rs265060	xxx	0.00009569	ALL	SUM	QUARTILE	8633	UNC5C	unc-5 homolog C (C. elegans)
4	137939936	rs17829074	xxx	0.000015	ALL	SUM	ADJUSTED	729578	LOC729578	hypothetical protein LOC729578
4	137939936	rs17829074	xxx	0.00001	ALL	SUM	QUARTILE	729578	LOC729578	hypothetical protein LOC729578
4	180158677	rs2167371	XXXXX	0.000004	anti-OMPC	LEVEL			BC043428	
4	185323707	rs2310044	xxx	0.000039	ALL	SUM	ADJUSTED	133121	ENPP6	ectonucleotide pyrophosphatase/phosphodiesterase 6
4	185323707	rs2310044	xxx	0.000011	ALL	SUM	QUARTILE	133121	ENPP6	ectonucleotide pyrophosphatase/phosphodiesterase 6
5	32028979	rs2052852	xxx	0.00009752	ASCA	PRESENCE ABSENCE		23037	PDZD2	PDZ domain containing 2
5	32028979	rs2052852	xxx	0.000027	IgG	PRESENCE ABSENCE		23037	PDZD2	PDZ domain containing 2
5	39154979	rs427829	xxx	0.00008501	IgA	LEVEL	LOGARITHMIC	2533	FYB	FYN binding protein (FYB-120/130)
5	76657430	rs3797462	xxx	0.00006927	anti-OMPC	PRESENCE ABSENCE		8622	PDE8B	phosphodiesterase 8B
5	80665128	rs6881927	xxx	0.00008685	anti-CBir1	LEVEL		134526	ACOT12	acyl-CoA thioesterase 12
5	92370602	rs2453759	xxx	0.00005472	IgG	LEVEL	LOGARITHMIC		BG204737	

FIG. 10E

5	117559122	rs2061882	xxx	0.00009235	ALL	SUM	QUARTILE		BX098718, BG208476	
5	133892498	rs329122	xxx	0.00006309	anti-CBir1	PRESENCE ABSENCE		23338	PHF15	PHD finger protein 15
5	138131165	rs851278	xxx	0.00005745	anti-CBir1	PRESENCE ABSENCE		1495	CTNNA1	catenin (cadherin-associated protein), alpha 1, 102kDa
5	138254666	rs176382	xxx	0.000031	anti-CBir1	PRESENCE ABSENCE		1495	CTNNA1	catenin (cadherin-associated protein), alpha 1, 102kDa
5	138269217	rs12719515	xxx	0.00004587	anti-CBir1	PRESENCE ABSENCE		1495	CTNNA1	catenin (cadherin-associated protein), alpha 1, 102kDa
5	141385691	rs163918	xxx	0.00008648	IgG	LEVEL	LOGARITHMIC	10007	GNPDA1	glucosamine-6-phosphate deaminase 1
5	147102213	rs6895278	xxx	0.00006039	IgG	LEVEL		9832	JAKMIP2	janus kinase and microtubule interacting protein 2
5	167753560	rs2112555	xxx	0.00006568	ALL	SUM	ADJUSTED	23286	WWC1	WW and C2 domain containing 1
5	167753560	rs2112555	xxx	0.00006126	ALL	SUM	QUARTILE	23286	WWC1	WW and C2 domain containing 1
5	174793846	rs265974	XXXXX	0.000005	ALL	SUM	ADJUSTED	1812	DRD1	dopamine receptor D1
5	174793846	rs265974	xxx	0.000026	ALL	SUM	QUARTILE	1812	DRD1	dopamine receptor D1
5	177611132	rs6422346	xxx	0.00008299	ALL	SUM	ADJUSTED	91522	COL23A1	collagen, type XXIII, alpha 1
5	177611132	rs6422346	xxx	0.00005096	ALL	SUM	QUARTILE	91522	COL23A1	collagen, type XXIII, alpha 1
6	461350	rs2493013	xxx	0.000036	anti-I2	PRESENCE ABSENCE		55770	EXOC2	exocyst complex component 2
6	7678861	rs6910759	XXXXX	0.000005	ALL	SUM	ADJUSTED	654	BMP6	bone morphogenetic protein 6

FIG. 10F

6	7678861	rs6910759	XXXXX	0.000009	ALL	SUM	QUARTILE	654	BMP6	bone morphogenetic protein 6
6	15174703	rs3846947	XXXXX	0.000001	anti-OMPC	LEVEL		728961	LOC728961	hypothetical protein LOC728961
6	16470367	rs179973		0.0001361	ALL	SUM	ADJUSTED	6310	ATXN1	ataxin 1
6	16470367	rs179973	xxx	0.00008447	ALL	SUM	QUARTILE	6310	ATXN1	ataxin 1
6	31164808	rs2523849	XXXXX	0.000002	IgG	LEVEL			FLJ37114	
6	31167273	rs2428514	xxx	0.00009132	IgG	PRESENCE ABSENCE			FLJ37114	
6	31167273	rs2428514	XXXXX	0.000001	IgG	LEVEL			FLJ37114	
6	31167273	rs2428514	xxx	0.000032	IgG	LEVEL	LOGARITHMIC		FLJ37114	
6	31222115	rs6917517	xxx	0.00006814	IgA	LEVEL		170679	CDSN,PSORS1C1	psoriasis susceptibility 1 candidate 1
6	31222115	rs6917517	xxx	0.00004338	IgG	LEVEL		170679	CDSN,PSORS1C1	psoriasis susceptibility 1 candidate 1
6	31222115	rs6917517	xxx	0.000038	IgG	LEVEL	LOGARITHMIC	170679	CDSN,PSORS1C1	psoriasis susceptibility 1 candidate 1
6	31223924	rs1042127	xxx	0.00006126	IgA	LEVEL		170679	CDSN,PSORS1C1	psoriasis susceptibility 1 candidate 1
6	31223924	rs1042127	xxx	0.000035	IgG	LEVEL		170679	CDSN,PSORS1C1	psoriasis susceptibility 1 candidate 1
6	31223924	rs1042127	xxx	0.000029	IgG	LEVEL	LOGARITHMIC	170679	CDSN,PSORS1C1	psoriasis susceptibility 1 candidate 1
6	31973245	rs644827	xxx	0.00007767	ALL	SUM	QUARTILE	80736	SLC44A4	solute carrier family 44, member 4
6	31974113	rs2242665	xxx	0.00007767	ALL	SUM	QUARTILE	80736	SLC44A4	solute carrier family 44, member 4
6	32057060	rs630379	xxx	0.00005789	IgG	LEVEL		7936	RDBP	RD RNA binding protein

FIG. 10G

6	32057060	rs630379	xxx	0.00005632	ALL	SUM	QUARTILE	7936	RDBP	RD RNA binding protein
6	32475662	rs3129963	xxx	0.00008147	IgG	PRESENCE ABSENCE		56244	BTNL2	butyrophilin-like 2 (MHC class II associated)
6	32477389	rs743862	XXXXX	0.000007	IgG	PRESENCE ABSENCE		56244	BTNL2	butyrophilin-like 2 (MHC class II associated)
6	32477389	rs743862	xxx	0.000015	IgG	LEVEL		56244	BTNL2	butyrophilin-like 2 (MHC class II associated)
6	32500379	rs2395174	xxx	0.00008483	IgG	PRESENCE ABSENCE		3122	HLA-DRA	major histocompatibility complex, class II, DR alpha
6	32507025	rs2239804	xxx	0.000037	IgG	LEVEL		3122	HLA-DRA	major histocompatibility complex, class II, DR alpha
6	32523248	rs9268832	xxx	0.00004767	IgG	PRESENCE ABSENCE		3122	HLA-DRA	major histocompatibility complex, class II, DR alpha
6	32721640	rs9275141	xxx	0.00005745	IgG	PRESENCE ABSENCE			HLA-DQB1	
6	32734983	rs2647012	xxx	0.00002	IgG	PRESENCE ABSENCE			HLA-DQB1	
6	36117361	rs851021	xxx	0.00005997	IgA	LEVEL		1432	MAPK14	mitogen-activated protein kinase 14
6	39227815	rs7773754	xxx	0.00006299	IgA	LEVEL			AK055788	
6	71974318	rs12661758	xxx	0.000015	IgG	LEVEL	LOGARITHMIC		DB234735	
6	71979436	rs9346446	xxx	0.00002	IgG	LEVEL	LOGARITHMIC		DB234735	
6	89961591	rs453561	xxx	0.00004499	ALL	SUM	ADJUSTED	2569	GABRR1	gamma-aminobutyric acid (GABA) receptor, rho 1
6	89961591	rs453561	xxx	0.000012	ALL	SUM	QUARTILE	2569	GABRR1	gamma-aminobutyric acid (GABA) receptor, rho 1

FIG. 10H

6	130053359	rs11154491	xxx	0.00007929	IgG	LEVEL		93663	ARHGAP18	Rho GTPase activating protein 18
6	147309970	rs7742400	XXXXX	0.000002	IgG	PRESENCE ABSENCE		729178	LOC729178	hypothetical protein LOC729178
6	147309970	rs7742400	xxx	0.000023	IgG	LEVEL		729178	LOC729178	hypothetical protein LOC729178
6	158331352	rs9459056	XXXXX	0.000004	IgA	LEVEL		8871	SYNJ2	synaptojanin 2
6	158331352	rs9459056	xxx	0.00005571	IgA	LEVEL	LOGARITHMIC	8871	SYNJ2	synaptojanin 2
6	167003680	rs6921577	xxx	0.00007339	anti-OMPC	LEVEL		6196	RPS6KA2	ribosomal protein S6 kinase, 90kDa, polypeptide 2
7	3735416	rs12701014	xxx	0.00004489	IgG	LEVEL		221935	SDK1	sidekick homolog 1, cell adhesion molecule (chicken)
7	31982261	rs7808892	xxx	0.00008556	anti-I2	PRESENCE ABSENCE		5137	PDE1C	phosphodiesterase 1C, calmodulin-dependent 70kDa
7	105510257	rs17153258	xxx	0.000059	anti-CBir1	LEVEL			AF086203	
7	105517818	rs6975426	xxx	0.00004896	anti-CBir1	LEVEL			AF086203	
7	153294558	rs4628181	xxx	0.0000518	anti-OMPC	PRESENCE ABSENCE		1804	DPP6	dipeptidyl-peptidase 6
8	3261623	rs6996823	xxx	0.00008214	anti-OMPC	LEVEL		64478	CSMD1	CUB and Sushi multiple domains 1
8	18425515	rs10090117	xxx	0.00004545	IgA	LEVEL		23362	PSD3	pleckstrin and Sec7 domain containing 3
8	23258190	rs11774789	xxx	0.00008475	ALL	SUM	ADJUSTED	4017	LOXL2	lysyl oxidase-like 2
8	24925353	rs2976456	XXXXX	0.000002	anti-OMPC	LEVEL		4747	NEFL	neurofilament, light polypeptide 68kDa
8	24987230	rs11135841	XXXXX	0.000001	anti-OMPC	LEVEL		4747	NEFL	neurofilament, light polypeptide 68kDa
8	38671914	rs7816405	XXXXX	0.000009	anti-CBir1	LEVEL			BX091769	
8	38691579	rs6983695	xxx	0.00006536	anti-CBir1	LEVEL			BX091769	

FIG. 10I

8	83590018	rs10504762	xxx	0.000015	IgG	LEVEL	LOGARITHMIC	389674	HNRPA1P4	heterogeneous nuclear ribonucleoprotein A1 pseudogene 4
8	108447077	rs2163870	xxx	0.00007678	IgG	LEVEL	LOGARITHMIC	284	ANGPT1	angiopoietin 1
8	108559172	rs951759	xxx	0.000028	IgG	PRESENCE ABSENCE		284	ANGPT1	angiopoietin 1
9	1028010	rs884101	xxx	0.000022	ALL	SUM	ADJUSTED	10655	DMRT2	doublesex and mab-3 related transcription factor 2
9	1028010	rs884101	xxx	0.000017	ALL	SUM	QUARTILE	10655	DMRT2	doublesex and mab-3 related transcription factor 2
9	1031524	rs2279989	xxx	0.000024	ALL	SUM	ADJUSTED	10655	DMRT2	doublesex and mab-3 related transcription factor 2
9	1031524	rs2279989	xxx	0.000019	ALL	SUM	QUARTILE	10655	DMRT2	doublesex and mab-3 related transcription factor 2
9	10468387	rs2784624	xxx	0.000029	IgA	PRESENCE ABSENCE		5789	PTPRD	protein tyrosine phosphatase, receptor type, D
9	10468387	rs2784624	XXXXX	0.000006	IgA	LEVEL		5789	PTPRD	protein tyrosine phosphatase, receptor type, D
9	10468387	rs2784624	xxx	0.000018	IgA	LEVEL	LOGARITHMIC	5789	PTPRD	protein tyrosine phosphatase, receptor type, D
9	28045900	rs1901565	xxx	0.000019	IgG	LEVEL			LRRN6C	
9	28045900	rs1901565	xxx	0.00004146	IgG	LEVEL	LOGARITHMIC		LRRN6C	
9	99945479	rs3760465	xxx	0.00006684	anti-CBir1	LEVEL		7464	CORO2A	coronin, actin binding protein, 2A
9	99953197	rs2795492	XXXXX	0.000001	anti-CBir1	LEVEL		7464	CORO2A	coronin, actin binding protein, 2A

FIG. 10J

9	116379698	rs10982300	xxx	0.00008998	anti-CBir1	PRESENCE ABSENCE		9550	ATP6V1G1	ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G1
9	116446202	rs2183018	xxx	0.00005848	anti-CBir1	PRESENCE ABSENCE		203197	C9orf91	chromosome 9 open reading frame 91
9	116446422	rs1058278	xxx	0.000039	anti-CBir1	PRESENCE ABSENCE		203197	C9orf91	chromosome 9 open reading frame 91
9	116447744	rs1058280	xxx	0.00005848	anti-CBir1	PRESENCE ABSENCE		203197	C9orf91	chromosome 9 open reading frame 91
9	129626509	rs3739817	xxx	0.00008403	anti-I2	LEVEL		2022	ENG	endoglin (Osler-Rendu-Weber syndrome 1)
9	129697654	rs3780670	xxx	0.000018	ALL	SUM	ADJUSTED	30815	ST6GALNAC6	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6
9	129697654	rs3780670	xxx	0.00004489	ALL	SUM	QUARTILE	30815	ST6GALNAC6	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6
9	136703513	rs4842139	xxx	0.00005391	anti-OMPC	LEVEL		1289	COL5A1	collagen, type V, alpha 1
9	137288987	rs7858253	xxx	0.00008155	IgG	LEVEL			BG437415	
9	137333104	rs10858383	xxx	0.000035	IgA	LEVEL	LOGARITHMIC		C9orf62	
9	137335350	rs10858385	xxx	0.00007984	ALL	SUM	ADJUSTED		C9orf62	
9	137335350	rs10858385	XXXXX	0.000005	IgA	LEVEL	LOGARITHMIC		C9orf62	
9	137335350	rs10858385	xxx	0.00008439	IgG	LEVEL	LOGARITHMIC		C9orf62	
10	4560425	rs10795184	xxx	0.00008978	anti-CBir1	LEVEL			CR749391	
10	33883553	rs2804875	xxx	0.000032	anti-OMPC	LEVEL		8829	NRP1	neuropilin 1

FIG. 10K

10	53478604	rs1871080	xxx	0.00009877	anti-CBir1	PRESENCE ABSENCE		5592	PRKG1	protein kinase, cGMP-dependent, type I
10	59174553	rs11591417	xxx	0.000025	anti-OMPC	LEVEL			CB269818	
10	59277608	rs6481369	xxx	0.00005006	anti-OMPC	LEVEL			CB269818	
10	73442768	rs730720	xxx	0.00004545	IgA	PRESENCE ABSENCE		9469	CHST3	carbohydrate (chondroitin 6) sulfotransferase 3
10	73445713	rs896076	xxx	0.000037	IgA	PRESENCE ABSENCE		9469	CHST3	carbohydrate (chondroitin 6) sulfotransferase 3
10	73445713	rs896076	xxx	0.00008667	IgA	LEVEL		9469	CHST3	carbohydrate (chondroitin 6) sulfotransferase 3
10	78964686	rs7921994	xxx	0.00008723	IgG	LEVEL	LOGARITHMIC	3778	KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1
10	78992459	rs2619641	xxx	0.00008574	ALL	SUM	ADJUSTED	3778	KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1
10	79750872	rs7920472	xxx	0.000026	ALL	SUM	ADJUSTED		AF086162	
10	79750872	rs7920472	xxx	0.00004566	ALL	SUM	QUARTILE		AF086162	
10	79936245	rs2099517	xxx	0.00007387	IgG	LEVEL			AF086162	
10	85122464	rs4418744	xxx	0.00009625	anti-OMPC	PRESENCE ABSENCE			AK056904	
10	133068612	rs3123221	xxx	0.00005115	IgG	LEVEL	LOGARITHMIC	256536	TCERG1L	transcription elongation regulator 1-like
11	1531644	rs7951820	xxx	0.00004756	ALL	SUM	ADJUSTED	81532	HCCA2	HCCA2 protein
11	1531644	rs7951820	xxx	0.00007828	ALL	SUM	QUARTILE	81532	HCCA2	HCCA2 protein

FIG. 10L

11	2459062	rs10832134	xxx	0.00009205	ALL	SUM	ADJUSTED	3784	KCNQ1	potassium voltage-gated channel, KQT-like subfamily, member 1
11	6216077	rs325702	xxx	0.000015	IgG	PRESENCE ABSENCE		1262	CNGA4-CCKBR	cyclic nucleotide gated channel alpha 4
11	6216077	rs325702	xxx	0.00005063	IgG	LEVEL		1262	CNGA4-CCKBR	cyclic nucleotide gated channel alpha 4
11	6216077	rs325702	XXXXX	0.000007	IgG	LEVEL	LOGARITHMIC	1262	CNGA4-CCKBR	cyclic nucleotide gated channel alpha 4
11	12925354	rs4469873	xxx	0.00004435	IgG	PRESENCE ABSENCE		7003	TEAD1	TEA domain family member 1 (SV40 transcriptional enhancer factor)
11	46447735	rs12574250	xxx	0.00009453	ASCA	PRESENCE ABSENCE		55626	FLJ20294	hypothetical protein FLJ20294
11	48069499	rs10501322	xxx	0.00007663	anti-OMPC	LEVEL		5795	PTPRJ	protein tyrosine phosphatase, receptor type, J
11	55420386	rs9943659	xxx	0.00007018	anti-OMPC	LEVEL		84767	SPRYD5	SPRY domain containing 5
11	55447435	rs7936086	xxx	0.00006873	anti-OMPC	LEVEL		10798	OR5I1	olfactory receptor, family 5, subfamily I, member 1
11	55452561	rs7115131	xxx	0.00006873	anti-OMPC	LEVEL		10798	OR5I1	olfactory receptor, family 5, subfamily I, member 1
11	55459537	rs9665861	xxx	0.00006873	anti-OMPC	LEVEL		10798	OR5I1	olfactory receptor, family 5, subfamily I, member 1
11	55460226	rs9666086	xxx	0.00006873	anti-OMPC	LEVEL		10798	OR5I1	olfactory receptor, family 5, subfamily I, member 1
11	74106228	rs968305	XXXXX	0.000005	IgA	PRESENCE ABSENCE		25884	CHRDL2	chordin-like 2
11	93190216	rs644009	xxx	0.00009533	IgG	LEVEL	LOGARITHMIC	9440	CRSP6	cofactor required for Sp1 transcriptional activation, subunit 6, 77kDa

FIG. 10M

11	99209253	rs7129269	xxx	0.00009501	ALL	SUM	QUARTILE	53942	CNTN5	contactin 5
11	104403053	rs557905	xxx	0.0000813	anti-I2	LEVEL		834	CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)
11	104409780	rs568910	xxx	0.000091	anti-I2	LEVEL		834	CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)
11	104417668	rs1503391	xxx	0.000091	anti-I2	LEVEL		114769	COP1	caspase-1 dominant-negative inhibitor pseudo-ICE
11	104423727	rs7934239	xxx	0.000028	anti-OMPC	LEVEL		114769	COP1	caspase-1 dominant-negative inhibitor pseudo-ICE
11	110504638	rs12276464	xxx	0.00005865	anti-OMPC	PRESENCE ABSENCE		5450	POU2AF1	POU domain, class 2, associating factor 1
11	130890705	rs385987	xxx	0.0000995	IgA	LEVEL		50863	HNT	neurotrimin
12	477487	rs12313707	xxx	0.00009886	ASCA	PRESENCE ABSENCE		283358	B4GALNT3	beta-1,4-N-acetyl-galactosaminyl transferase 3
12	477487	rs12313707	xxx	0.000028	IgA	PRESENCE ABSENCE		283358	B4GALNT3	beta-1,4-N-acetyl-galactosaminyl transferase 3
12	7440276	rs4072797	xxx	0.00004525	IgG	LEVEL		283316	CD163L1	CD163 molecule-like 1
12	10742925	rs2166066	xxx	0.00008122	IgG	LEVEL	LOGARITHMIC	8531	CSDA	cold shock domain protein A
12	10761665	rs3816566	xxx	0.0000979	ALL	SUM	QUARTILE	8531	CSDA	cold shock domain protein A
12	46326141	rs1153978	xxx	0.000032	IgG	LEVEL			FLJ21908	
12	46326141	rs1153978	xxx	0.000015	IgG	LEVEL	LOGARITHMIC		FLJ21908	
12	46337723	rs948393	xxx	0.00008742	IgG	LEVEL			FLJ21908	

FIG. 10N

12	46337723	rs948393	xxx	0.0000479	IgG	LEVEL	LOGARITHMIC		FLJ21908	
12	92237010	rs6538408	XXXXX	0.000005	IgG	LEVEL		11163	NUDT4	nudix (nucleoside diphosphate linked moiety X)-type motif 4
12	97719929	rs1477237	xxx	0.00009047	anti-CBir1	LEVEL		56899	ANKS1B	ankyrin repeat and sterile alpha motif domain containing 1B
12	97719929	rs1477237	xxx	0.0000978	ALL	SUM	ADJUSTED	56899	ANKS1B	ankyrin repeat and sterile alpha motif domain containing 1B
12	97719929	rs1477237	xxx	0.00007533	ALL	SUM	QUARTILE	56899	ANKS1B	ankyrin repeat and sterile alpha motif domain containing 1B
12	105877725	rs10746071	xxx	0.00004306	anti-I2	LEVEL			C12orf23,LOC728705	
12	117225058	rs468574	xxx	0.00009466	IgA	LEVEL	LOGARITHMIC	51347	TAOK3	TAO kinase 3
13	22838710	rs6490792	xxx	0.00005153	IgA	LEVEL		26278	SACS	spastic ataxia of Charlevoix-Saguenay (sacsin)
13	107034232	rs1998564	xxx	0.00005944	anti-CBir1	LEVEL		728215	LOC728215	similar to transmembrane protein 28
14	22967306	rs1951154	xxx	0.00006088	ALL	SUM	QUARTILE	4625	MYH7	myosin, heavy chain 7, cardiac muscle, beta
14	29657679	rs8011977	xxx	0.000033	IgG	LEVEL	LOGARITHMIC	5587	PRKD1	protein kinase D1
14	29663179	rs7152980	xxx	0.00007561	IgG	LEVEL		5587	PRKD1	protein kinase D1
14	29663179	rs7152980	xxx	0.000024	IgG	LEVEL	LOGARITHMIC	5587	PRKD1	protein kinase D1
14	62259523	rs11158449	xxx	0.00007913	IgG	PRESENCE ABSENCE		27133	KCNH5	potassium voltage-gated channel, subfamily H (eag-related), member 5
15	37145001	rs990579	xxx	0.00004008	anti-OMPC	LEVEL			FLJ39531	
15	59900432	rs8023523	xxx	0.000016	IgA	LEVEL		54832	VPS13C	vacuolar protein sorting 13 homolog C (S. cerevisiae)

FIG. 10O

15	59900432	rs8023523	xxx	0.00009602	IgA	LEVEL	LOGARITHMIC	54832	VPS13C	vacuolar protein sorting 13 homolog C (S. cerevisiae)
15	78491816	rs1446337	XXXXX	0.000008	IgG	PRESENCE ABSENCE		9915	ARNT2	aryl-hydrocarbon receptor nuclear translocator 2
15	90816282	rs1455775	xxx	0.0000489	ALL	SUM	ADJUSTED	145858	C15orf32	chromosome 15 open reading frame 32
15	90816282	rs1455775	xxx	0.00009975	ALL	SUM	QUARTILE	145858	C15orf32	chromosome 15 open reading frame 32
15	94629190	rs8033891	xxx	0.000031	anti-OMPC	LEVEL			FLJ10010	
15	94641189	rs4984430	XXXXX	0.000004	anti-OMPC	LEVEL			FLJ10010	
16	6276738	rs716509	xxx	0.000028	IgA	PRESENCE ABSENCE		54715	A2BP1	ataxin 2-binding protein 1
16	6276738	rs716509	xxx	0.00009355	IgA	LEVEL	LOGARITHMIC	54715	A2BP1	ataxin 2-binding protein 1
16	7169331	rs1922587	xxx	0.0000409	IgG	PRESENCE ABSENCE		54715	A2BP1	ataxin 2-binding protein 1
16	7175014	rs1922589	xxx	0.000037	IgG	PRESENCE ABSENCE		54715	A2BP1	ataxin 2-binding protein 1
16	27047330	rs4787923	XXXXX	0.000009	IgG	LEVEL		3566	IL4R	interleukin 4 receptor
16	27900129	rs8054996	xxx	0.00005298	anti-OMPC	LEVEL			UNQ5831	
16	27910722	rs4788025	xxx	0.000024	anti-I2	LEVEL			UNQ5831	
16	72153219	rs825688	xxx	0.000019	ALL	SUM	ADJUSTED		ng	
16	72163783	rs825678	xxx	0.00009183	anti-I2	PRESENCE ABSENCE			ng	
16	77869647	rs9806910	xxx	0.00008732	IgG	PRESENCE ABSENCE		51741	WWOX	WW domain containing oxidoreductase
16	80357386	rs10445097	xxx	0.00007241	IgG	LEVEL		5336	PLCG2	phospholipase C, gamma 2 (phosphatidylinositol-specific)

FIG. 10P

16	80357386	rs10445097	XXXXX	0.000009	IgG	LEVEL	LOGARITHMIC	5336	PLCG2	phospholipase C, gamma 2 (phosphatidylinositol-specific)
17	23731073	rs2027993	xxx	0.0000773	IgG	PRESENCE ABSENCE		23098	SARM1	sterile alpha and TIR motif containing 1
17	35485379	rs939348	xxx	0.00005168	IgG	LEVEL		7067	THRA	thyroid hormone receptor, alpha (erythroblastic leukemia viral (v-erb-a) oncogene homolog, avian)
17	39410265	rs918242	xxx	0.000024	anti-OMPC	PRESENCE ABSENCE		5697	PYY	peptide YY
17	62233006	rs7342847	xxx	0.00005208	IgG	PRESENCE ABSENCE		5578	PRKCA	protein kinase C, alpha
17	62233006	rs7342847	XXXXX	0.000007	IgG	LEVEL		5578	PRKCA	protein kinase C, alpha
17	72147848	rs8069024	xxx	0.000026	IgG	LEVEL		55808	ST6GALNAC1	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 1
17	72173649	rs9897045	xxx	0.0000495	IgG	LEVEL		55808	ST6GALNAC1	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 1
18	4012527	rs4798157	xxx	0.000024	IgG	PRESENCE ABSENCE		388458	LOC388458	hypothetical gene supported by BC040718
18	4015719	rs1442385	xxx	0.000019	IgG	PRESENCE ABSENCE		388458	LOC388458	hypothetical gene supported by BC040718
18	4016587	rs1372631	xxx	0.00004197	ASCA	PRESENCE ABSENCE		388458	LOC388458	hypothetical gene supported by BC040718

FIG. 10Q

18	4016587	rs1372631	xxx	0.00006557	IgA	LEVEL		388458	LOC388458	hypothetical gene supported by BC040718
18	4016587	rs1372631	XXXXX	0.000001	IgG	PRESENCE ABSENCE		388458	LOC388458	hypothetical gene supported by BC040718
18	4016587	rs1372631	xxx	0.000028	IgG	LEVEL	LOGARITHMIC	388458	LOC388458	hypothetical gene supported by BC040718
18	8872679	rs8094017	xxx	0.000021	ASCA	PRESENCE ABSENCE		23255	KIAA0802	KIAA0802
18	8872679	rs8094017	xxx	0.0000616	IgG	PRESENCE ABSENCE		23255	KIAA0802	KIAA0802
18	8872679	rs8094017	xxx	0.000036	IgG	LEVEL	LOGARITHMIC	23255	KIAA0802	KIAA0802
18	11807585	rs12454673	xxx	0.00004082	IgG	LEVEL	LOGARITHMIC	2774	GNAL	guanine nucleotide binding protein (G protein), alpha activating activity polypeptide, olfactory type
18	20752168	rs1786153	xxx	0.00007105	anti-I2	PRESENCE ABSENCE		25925	ZNF521	zinc finger protein 521
18	51958209	rs1789588	xxx	0.000028	anti-I2	PRESENCE ABSENCE		642484	FLJ45743	hypothetical protein LOC642484
18	63184658	rs9951011	xxx	0.00006993	IgA	LEVEL		92126	DSEL	dermatan sulfate epimerase-like
18	63300140	rs1061568	xxx	0.00005764	ALL	SUM	ADJUSTED	92126	DSEL	dermatan sulfate epimerase-like
18	63483660	rs7244904	xxx	0.00006345	IgG	LEVEL	LOGARITHMIC	92126	DSEL	dermatan sulfate epimerase-like
18	65301877	rs1036837	xxx	0.00009153	anti-I2	PRESENCE ABSENCE		220164	DOK6	docking protein 6
18	65301877	rs1036837	xxx	0.00006067	ALL	SUM	ADJUSTED	220164	DOK6	docking protein 6
19	2872008	rs8108501	xxx	0.000027	IgA	LEVEL		58492	ZNF77	zinc finger protein 77
19	2884480	rs3786948	xxx	0.00008677	IgA	LEVEL		58492	ZNF77	zinc finger protein 77

FIG. 10R

19	3055629	rs308052	xxx	0.0000551	ASCA	PRESENCE ABSENCE		2767	GNA11	guanine nucleotide binding protein (G protein), alpha 11 (Gq class)
19	17887794	rs4808716	xxx	0.00006844	IgA	PRESENCE ABSENCE		115098	CCDC124	coiled-coil domain containing 124
19	19164802	rs1050483	xxx	0.000021	IgA	LEVEL	LOGARITHMIC	8625	RFXANK	regulatory factor X-associated ankyrin-containing protein
19	19196083	rs2238672	xxx	0.00004772	IgA	PRESENCE ABSENCE		1463	NCAN	neurocan
19	19196083	rs2238672	xxx	0.00006542	IgA	LEVEL	LOGARITHMIC	1463	NCAN	neurocan
19	34854335	rs10424881	xxx	0.00009732	anti-CBir1	PRESENCE ABSENCE		79156	PLEKHF1	pleckstrin homology domain containing, family F (with FYVE domain) member 1
19	35631829	rs33431	xxx	0.00004032	ASCA	PRESENCE ABSENCE		9745	ZNF536	zinc finger protein 536
19	45141888	rs2231738	xxx	0.00004603	IgA	LEVEL		5704	PSMC4	proteasome (prosome, macropain) 26S subunit, ATPase, 4
19	45169305	rs234370	xxx	0.00007812	IgA	LEVEL		5704	PSMC4	proteasome (prosome, macropain) 26S subunit, ATPase, 4
19	45172763	rs371500	xxx	0.00005261	IgA	LEVEL		5704	PSMC4	proteasome (prosome, macropain) 26S subunit, ATPase, 4
19	45181310	rs8105066	xxx	0.00006768	IgA	LEVEL		5704	PSMC4	proteasome (prosome, macropain) 26S subunit, ATPase, 4
19	45253015	rs459091	xxx	0.000028	IgA	LEVEL			ZNF780B	
19	57313456	rs8111640	xxx	0.0000789	anti-I2	PRESENCE ABSENCE		90317	ZNF616	zinc finger protein 616

FIG. 10S

19	62414825	rs917340	xxx	0.00005952	IgG	LEVEL	LOGARITHMIC	9422	ZNF264	zinc finger protein 264
20	12937901	rs3761896	xxx	0.000017	anti-OMPC	LEVEL		55304	SPTLC3	serine palmitoyltransferase, long chain base subunit 3
20	14748958	rs6034046	xxx	0.000011	anti-OMPC	LEVEL		140733	C20orf133	chromosome 20 open reading frame 133
20	17411917	rs6044842	xxx	0.00008138	ASCA	PRESENCE ABSENCE		5126	PCSK2	proprotein convertase subtilisin/kexin type 2
20	21729363	rs6047633	XXXXX	0.000006	ASCA	PRESENCE ABSENCE		5075	PAX1	paired box gene 1
20	21729363	rs6047633	XXXXX	0.000006	IgG	PRESENCE ABSENCE		5075	PAX1	paired box gene 1
20	21729363	rs6047633	xxx	0.00003	IgG	LEVEL	LOGARITHMIC	5075	PAX1	paired box gene 1
20	21733073	rs6047637	xxx	0.00006768	ASCA	PRESENCE ABSENCE		5075	PAX1	paired box gene 1
20	21897593	rs6106434	xxx	0.00006417	ASCA	PRESENCE ABSENCE		5075	PAX1	paired box gene 1
20	52435022	rs6023181	xxx	0.000017	ASCA	PRESENCE ABSENCE		55816	DOK5	docking protein 5
20	52435022	rs6023181	XXXXX	0.000008	IgG	PRESENCE ABSENCE		55816	DOK5	docking protein 5
20	52435022	rs6023181	XXXXX	0.000003	IgG	LEVEL		55816	DOK5	docking protein 5
20	52435022	rs6023181	xxx	0.000018	IgG	LEVEL	LOGARITHMIC	55816	DOK5	docking protein 5
20	52470314	rs6023227	XXXXX	0.000004	ASCA	PRESENCE ABSENCE		55816	DOK5	docking protein 5
20	52470314	rs6023227	xxx	0.00005764	IgA	LEVEL		55816	DOK5	docking protein 5
20	52470314	rs6023227	xxx	0.000033	IgG	PRESENCE ABSENCE		55816	DOK5	docking protein 5
20	52470314	rs6023227	xxx	0.000021	IgG	LEVEL		55816	DOK5	docking protein 5
20	52470314	rs6023227	xxx	0.000017	IgG	LEVEL	LOGARITHMIC	55816	DOK5	docking protein 5

FIG. 10T

20	56807638	rs6100226	xxx	0.00004866	IgA	LEVEL		2778	GNAS	GNAS complex locus
20	56807638	rs6100226	xxx	0.00004525	ALL	SUM	QUARTILE	2778	GNAS	GNAS complex locus
20	59971956	rs6061396	xxx	0.000013	anti-OMPC	PRESENCE ABSENCE		6874	TAF4	TAF4 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 135kDa
20	59997019	rs6089583	xxx	0.00006868	anti-OMPC	PRESENCE ABSENCE		6874	TAF4	TAF4 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 135kDa
21	33454426	rs2834115	xxx	0.000021	anti-OMPC	PRESENCE ABSENCE			BC105117	
21	33539959	rs2834159	xxx	0.00005556	anti-CBir1	PRESENCE ABSENCE		3455	IFNAR2	interferon (alpha, beta and omega) receptor 2
22	22476629	rs9620326	xxx	0.0000554	IgG	LEVEL		6598	SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1
22	34773651	rs6000083	xxx	0.00008819	IgG	PRESENCE ABSENCE		23543	RBM9	RNA binding motif protein 9
22	37062770	rs13054361	xxx	0.000022	IgA	PRESENCE ABSENCE		730115	LOC730115	hypothetical protein LOC730115
22	37062770	rs13054361	xxx	0.00005208	ALL	SUM	QUARTILE	730115	LOC730115	hypothetical protein LOC730115
22	46585519	rs10854841	xxx	0.00005548	ALL	SUM	QUARTILE		FLJ35788	

FIG. 11A

No	CHR	SNP	A1	F_A	F_U	A2	CHISQ	P	OR	Location	Gene Name	Comments
174	12	rs2682292	C	0.3796	0.4363	A	7.08	0.007805	0.7904	51626209	KRT8/KRT18	keratin 8 & keratin 18
93	6	rs367398	A	0.3864	0.3337	G	6.57	0.01039	1.257	32299708	Chr6 Mapping	Notch 4
173	12	rs12423065	A	0.3821	0.4358	G	6.39	0.01147	0.8008	51625301	KRT8/KRT18	keratin 8 & keratin 18
97	6	rs9296012	A	0.208	0.167	G	6.18	0.0129	1.31	32303310	Chr6 Mapping	Notch 4
229	14	rs4982753	A	0.3062	0.2594	G	5.98	0.01451	1.26	22884409	Chr14 Mapping	solute carrier family 22 (organic cation)
159	12	rs2853564	G	0.4264	0.3754	A	5.91	0.01509	1.237	46564754	VDR	vitamin D receptor
168	12	rs12580050	T	0.3463	0.3966	A	5.8	0.01601	0.806	51586470	KRT8/KRT18	keratin 8 & keratin 18
176	12	rs2070876	A	0.354	0.4037	G	5.62	0.01775	0.8096	51631097	KRT8/KRT18	keratin 8 & keratin 18
252	14	rs178634	G	0.1062	0.07839	C	5.27	0.02173	1.397	22919839	CMTM5	chemokine-like factor superfamily 5 isoform a
214	14	rs2025210	A	0.1202	0.1539	C	5.02	0.02505	0.7506	22333978	SLC7A7	solute carrier family 7 (cationic acid)
215	14	rs5027249	G	0.1757	0.214	A	4.93	0.02637	0.7827	22340436	SLC7A7	solute carrier family 7 (cationic acid)
172	12	rs2172276	G	0.3523	0.3982	A	4.82	0.0282	0.822	51624308	KRT8/KRT18	keratin 8 & keratin 18
78	5	rs2853694	C	0.4276	0.474	A	4.68	0.0305	0.8292	158681666	IL12B	interleukin 12 beta
141	12	rs1461567	A	0.2687	0.3104	G	4.5	0.03389	0.8164	42450956	IRAK4	interleukin-1 receptor-associated kinase 4
246	14	rs11465506	A	0.0065	0.01674	G	4.17	0.04108	0.3849	22912501	IL25	interleukin 25
269	14	rs10146843	C	0.3805	0.3391	G	4.07	0.04374	1.197	23472852	Chr14 Mapping	C14orf165
157	12	rs2254210	A	0.3769	0.3357	G	4.05	0.04418	1.197	46559981	VDR	vitamin D receptor
31	1	rs1569922	A	0.3057	0.3462	G	4	0.0456	0.8314	67376984	IL23R	interleukin 23 receptor
129	10	rs570613	G	0.3385	0.3794	A	3.91	0.04814	0.8369	8146508	GATA3	GATA binding protein 3 isoform 1
106	6	rs7747909	A	0.2571	0.222	G	3.73	0.05334	1.213	52162208	IL17	
289	19	rs5030390	A	0.0687	0.09177	G	3.72	0.05384	0.7295	10243537	ICAM1	
46	3	rs11919639	C	0.0452	0.06416	A	3.53	0.06024	0.6908	113691440	BTLA	Questionable but WORK
142	12	rs4251501	C	0.0116	0.02268	A	3.48	0.06195	0.507	42457911	IRAK4	Questionable but WORK
300	21	rs2284553	A	0.3536	0.3926	G	3.48	0.06212	0.8465	33698565	IFNGR2	
15	1	rs2229579	A	0.1266	0.1019	G	3.4	0.06503	1.278	23946468	CNR2	
283	19	rs2279627	G	0.2158	0.2494	C	3.38	0.06608	0.8278	6614594	TNFSF14 (LIGHT)	
213	14	rs8006372	G	0.4044	0.3673	A	3.18	0.07465	1.17	22329539	Chr14 Mapping	
165	12	rs4351899	A	0.5247	0.4872	C	3.03	0.08176	1.162	51581088	KRT8/KRT18	

FIG. 11B

105	6	rs10484879	A	0.2532	0.2218	C	3.01	0.08257	1.19	52159916	IL17	
167	12	rs2035875	A	0.5233	0.4861	G	2.99	0.08385	1.16	51582184	KRT8/KRT18	
37	1	rs2201841	G	0.4028	0.3671	A	2.94	0.08648	1.163	67406223	IL23R	
85	6	rs2854050	A	0.0788	0.1001	G	2.9	0.08888	0.769	32293583	Chr6 Mapping	Questionable but WORK
74	4	rs3774968	A	0.474	0.4378	G	2.87	0.09055	1.157	103888305	NFKB1	
137	12	rs2078178	A	0.2248	0.2561	G	2.85	0.0912	0.8424	10167829	CLEC7A (Dectin)	
45	3	rs2705534	C	0.0827	0.104	A	2.79	0.09482	0.7767	113691075	BTLA	
158	12	rs2238136	A	0.239	0.2705	G	2.78	0.09554	0.8472	46563980	VDR	

FIG. 12A

CHR	SNP	A1	F_A	F_U	A2	CHISQ	P	OR	Location	Gene Name	Comments
6	rs415929	G	0.4236	0.3634	A	8.307	0.00395	1.287	32297010	Chr6 Mapping	Notch 4
1	rs2863212	G	0.06865	0.1039	A	7.93	0.00486	0.636	67397137	IL23R	Interleukin 23 receptor
6	rs367398	A	0.3877	0.3331	G	7.039	0.00798	1.268	32299708	Chr6 Mapping	Notch 4
14	rs178634	G	0.107	0.0781	C	5.665	0.01731	1.415	22919839	CMTM5	chemokine-like factor superfamily 5 isoform a
12	rs2853564	G	0.4249	0.3761	A	5.404	0.02009	1.225	46564754	VDR	vitamin D receptor
12	rs7298416	A	0.1218	0.1564	G	5.193	0.02267	0.748	10177251	CLEC7A (Dectin)	dendritic cell-associated C-type lectin 1
14	rs12889813	A	0.285	0.2425	G	5.126	0.02357	1.245	23376377	Chr14 Mapping	C14orf165
12	rs10783219	T	0.3109	0.3558	A	4.85	0.02765	0.817	46581755	VDR	vitamin D receptor
19	rs2306190	C	0.3744	0.4203	A	4.725	0.02972	0.825	14023676	IL27RA	Interleukin 23 receptor alpha subunit
12	rs2254210	A	0.3792	0.3348	G	4.696	0.03023	1.214	46559981	VDR	vitamin D receptor
6	rs6907458	A	0.07772	0.0556	G	4.533	0.03325	1.433	32279266	Chr6 Mapping	Notch 4
4	rs2227306	A	0.364	0.4087	G	4.532	0.03327	0.828	74972090	IL8	interleukin 8
12	rs11053624	G	0.07143	0.0969	A	4.307	0.03795	0.717	10174978	CLEC7A (Dectin)	dendritic cell-associated C-type lectin 1
22	rs721930	G	0.2318	0.1971	C	3.935	0.0473	1.229	15960362	IL17R	interleukin 17 receptor
6	rs9296012	A	0.2021	0.1696	G	3.875	0.04902	1.24	32303310	Chr6 Mapping	Notch 4
4	rs11730667	G	0.4054	0.447	A	3.797	0.05134	0.844	74965246	IL8	
22	rs2041629	A	0.1995	0.168	G	3.686	0.05487	1.234	15931698	IL17R	
12	rs2238136	A	0.2358	0.2718	G	3.65	0.05605	0.826	46563980	VDR	
4	rs2227307	C	0.3964	0.4369	A	3.645	0.05624	0.846	74971704	IL8	
14	rs178633	C	0.03368	0.021	G	3.602	0.05771	1.625	22907989	Chr14 Mapping	
14	rs6572754	A	0.2085	0.2428	G	3.558	0.05926	0.822	22327900	Chr14 Mapping	
6	rs7747909	A	0.2565	0.2223	G	3.531	0.06022	1.206	52162208	IL17	
6	rs9267845	T	0.4547	0.4147	A	3.526	0.06042	1.177	32301676	Chr6 Mapping	
21	rs2284553	A	0.3536	0.3926	G	3.48	0.06212	0.847	33698565	IFNGR2	
22	rs2241049	G	0.386	0.3476	A	3.473	0.06238	1.18	15962234	IL17R	
4	rs4694637	G	0.4016	0.4408	A	3.392	0.0655	0.851	74977869	IL8	
6	rs9267853	A	0.2448	0.2799	G	3.377	0.06613	0.834	32303229	Chr6 Mapping	

FIG. 12B

22	rs9606603	A	0.4896	0.4508	T	3.287	0.06983	1.169	15936067	IL17R
4	rs4694178	C	0.4016	0.4392	A	3.137	0.07652	0.857	74977723	IL8
19	rs2277984	A	0.4663	0.5039	G	3.052	0.08062	0.86	6630511	TNFSF14 (LIGHT)

FIG. 13A

No	CHR	SNP	A1	F_A	F_U	A2	CHISQ	P	OR	Location	Gene Name	Comments
15	1	rs2229579	A	0.133	0.09944	G	6.287	0.01216	1.389	23946468	CNR2	Cannabinoid receptor 2 (macrophage)
19	1	rs16828926	A	0.188	0.1454	G	7.423	0.006439	1.361	23960436	CNR2	Cannabinoid receptor 2 (macrophage)
20	1	rs2501390	A	0.1905	0.1467	G	7.809	0.0052	1.37	23961102	CNR2	Cannabinoid receptor 2 (macrophage)
21	1	rs2502959	A	0.1931	0.1548	C	5.757	0.01642	1.306	23962167	CNR2	Cannabinoid receptor 2 (macrophage)
22	1	rs2502965	G	0.1905	0.1471	A	7.662	0.00564	1.365	23963582	CNR2	Cannabinoid receptor 2 (macrophage)
93	6	rs367398	A	0.3827	0.3352	G	5.38	0.02037	1.23	32299708	Chr6 Mapping	Notch 4
95	6	rs9267845	T	0.4629	0.4121	A	5.744	0.01654	1.229	32301676	Chr6 Mapping	Notch 4
97	6	rs9296012	A	0.2174	0.1632	G	10.89	0.0009669	1.425	32303310	Chr6 Mapping	Notch 4
141	12	rs1461567	A	0.257	0.3165	G	9.193	0.00243	0.7472	42450956	IRAK4	interleukin-1 receptor-associated kinase 4
203	14	rs8013531	A	0.4038	0.4544	G	5.657	0.01739	0.8132	22317527	SLC7A7	solute carrier family 7 (cationic amino acid)
258	14	rs12435647	A	0.1394	0.1809	G	6.716	0.009554	0.7333	23379705	Chr14 Mapping	C14orf165
290	19	rs281432	C	0.455	0.5039	G	5.193	0.02268	0.822	10251658	ICAM1	intercellular adhesion molecule 1
307	22	rs2241042	A	0.4118	0.3667	C	4.705	0.03008	1.209	15942253	IL17R	interleukin 17 receptor
6	1	rs3007421	A	0.1113	0.1428	G	4.692	0.03031	0.7516	6464455	TNFRSF25 (DR3)	tumor necrosis factor receptor superfamily
194	14	rs7785	A	0.06905	0.04828	G	4.562	0.03269	1.462	20014854	Chr14 Mapping	NP-purine nucleoside phosphorylase
128	10	rs1399180	A	0.1195	0.1513	G	4.507	0.03375	0.7613	8138725	GATA3	GATA binding protein 3 isoform 1
216	14	rs12884337	A	0.3299	0.3733	G	4.458	0.03474	0.8265	22342954	SLC7A7	solute carrier family 7 (cationic amino acid)
130	10	rs528778	A	0.1471	0.1809	G	4.415	0.03562	0.7806	8152149	GATA3	GATA binding protein 3 isoform 1
213	14	rs8006372	G	0.3491	0.3918	A	4.222	0.03991	0.8326	22329539	SLC7A7	solute carrier family 7 (cationic amino acid)
4	1	rs2986754	C	0.06795	0.09232	G	4.158	0.04143	0.7167	6460731	TNFRSF25 (DR3)	tumor necrosis factor receptor superfamily
7	1	rs2986753	G	0.1121	0.1413	A	4.023	0.04488	0.7671	6464701	TNFRSF25 (DR3)	tumor necrosis factor receptor superfamily
244	14	rs10149449	G	0.08312	0.1088	A	3.951	0.04685	0.7428	22910351	IL25	interleukin 25
42	3	rs1982809	G	0.2046	0.24	A	3.865	0.0493	0.8146	113665430	BTLA	B and T lymphocyte associated
44	3	rs9288953	A	0.2877	0.3267	G	3.832	0.05027	0.8326	113685942	BTLA	B and T lymphocyte associated
46	3	rs11919639	C	0.04476	0.06437	A	3.814	0.05083	0.681	113691440	BTLA	B and T lymphocyte associated
41	1	rs1343151	A	0.2596	0.2952	G	3.403	0.06509	0.837	67431150	IL23R	
190	14	rs1713460	G	0.3141	0.2786	A	3.341	0.06757	1.186	20003455	Chr14 Mapping	
80	6	rs6907458	A	0.07584	0.05681	G	3.34	0.06761	1.362	32279266	Chr6 Mapping	

FIG. 13B

78	5	rs2853694	C	0.4335	0.4722	A	3.29	0.06972	0.8553	158681666	IL12B	
5	1	rs3007420	G	0.05256	0.07183	C	3.274	0.07041	0.7169	6464089	TNFRSF25 (DR3)	
118	9	rs7847158	G	0.2295	0.2628	A	3.197	0.07378	0.8355	114639819	TNFSF15 (TL1A)	Questionable but WORK
31	1	rs1569922	A	0.309	0.3446	G	3.11	0.07783	0.8503	67376984	IL23R	
90	6	rs915895	A	0.2059	0.2375	G	3.101	0.07827	0.8323	32298195	Chr6 Mapping	Questionable but WORK
91	6	rs443198	G	0.4284	0.3917	A	3.056	0.08043	1.164	32298384	Chr6 Mapping	
96	6	rs9267853	A	0.2455	0.2783	G	2.989	0.08386	0.8438	32303229	Chr6 Mapping	
37	1	rs2201841	G	0.4026	0.3667	A	2.984	0.08409	1.164	67406223	IL23R	

FIG. 14

CHR	SNP	A1	F_A	F_U	A2	CHISQ	P	OR	Location	Gene Name	Comments
6	rs9296012	A	0.2008	0.1581	G	7.983	0.004721	1.338	32303310	Chr6 Mapping	Notch 4
22	rs2241042	A	0.4068	0.3536	C	7.751	0.005369	1.254	15942253	IL17R	interleukin 17 receptor
12	rs1461567	A	0.275	0.3222	G	6.838	0.008925	0.7983	42450956	IRAK4	interleukin-1 receptor-associated kinase 4
10	rs528778	A	0.1523	0.1893	G	6.229	0.01256	0.7697	8152149	GATA3	GATA binding protein 3 isoform 1
22	rs9606603	A	0.4854	0.4393	T	5.521	0.01879	1.204	15936067	IL17R	interleukin 17 receptor
22	rs882643	C	0.1162	0.1456	G	4.939	0.02625	0.7709	15966377	IL17R	interleukin 17 receptor
1	rs11209008	A	0.01923	0.03271	G	4.647	0.0311	0.5798	67335319	IL23R	interleukin 23 receptor
10	rs1399180	A	0.1269	0.1565	G	4.598	0.03201	0.7837	8138725	GATA3	GATA binding protein 3 isoform 1
12	rs3858733	C	0.03769	0.0234	A	4.445	0.03501	1.635	46524234	VDR	vitamin D receptor
9	rs7847158	G	0.2349	0.2707	A	4.356	0.03688	0.8274	114639819	TNFSF15 (TL1A)	tl1a
3	rs2705534	C	0.08538	0.109	A	4.12	0.04239	0.7628	113691075	BTLA	B and T lymphocyte associated
4	rs2227306	A	0.3775	0.4159	G	3.974	0.04621	0.8517	74972090	IL8	interleukin 8
3	rs2633582	C	0.08538	0.1083	A	3.867	0.04926	0.769	113702030	BTLA	B and T lymphocyte associated
21	rs9808753	G	0.1523	0.1262	A	3.681	0.05504	1.244	33709182	IFNGR2	
19	rs8106574	A	0.2092	0.2407	G	3.66	0.05574	0.8349	6622142	TNFSF14 (LIGHT)	
10	rs1244186	A	0.2231	0.2547	G	3.548	0.05962	0.8403	8132689	GATA3	
1	rs2986751	A	0.06857	0.08814	G	3.425	0.06421	0.7616	6469047	TNFRSF25 (DR3)	
1	rs2986754	C	0.07538	0.09468	G	3.086	0.07895	0.7796	6460731	TNFRSF25 (DR3)	
14	rs8017550	G	0.05932	0.04439	C	2.924	0.08727	1.358	22910159	Chr14 Mapping	
21	rs11088251	C	0.1477	0.1248	A	2.872	0.09015	1.215	33692680	IFNGR2	
6	rs6907458	A	0.07043	0.05459	G	2.734	0.09826	1.312	32279266	Chr6 Mapping	
1	rs3007420	G	0.05796	0.0741	C	2.723	0.09893	0.7687	6464089	TNFRSF25 (DR3)	
1	rs3007421	A	0.1223	0.1443	G	2.705	0.1	0.8263	6464455	TNFRSF25 (DR3)	

FIG. 15A

CHR	SNP	A1	F_A	F_U	A2	CHISQ	P	OR	Location	Gene Name	Comments
6	rs415929	G	0.4236	0.3634	A	8.307	0.003949	1.287	32297010	Chr6 Mapping	Notch 4
1	rs2863212	G	0.06865	0.1039	A	7.93	0.004862	0.636	67397137	IL23R	interleukin 23 receptor
6	rs367398	A	0.3877	0.3331	G	7.039	0.007976	1.268	32299708	Chr6 Mapping	Notch 4
14	rs178634	G	0.107	0.07813	C	5.665	0.01731	1.415	22919839	CMTM5	chemokine-like factor superfamily 5 isoform a
12	rs2853564	G	0.4249	0.3761	A	5.404	0.02009	1.225	46564754	VDR	vitamin D receptor
12	rs7298416	A	0.1218	0.1564	G	5.193	0.02267	0.7481	10177251	CLEC7A (Dectin)	dendritic cell-associated C-type lectin 1
14	rs12889813	A	0.285	0.2425	G	5.126	0.02357	1.245	23376377	Chr14 Mapping	unknown gene
12	rs10783219	T	0.3109	0.3558	A	4.85	0.02765	0.8168	46581755	VDR	vitamin D receptor
19	rs2306190	C	0.3744	0.4203	A	4.725	0.02972	0.8254	14023676	IL27RA	interleukin 27 receptor
12	rs2254210	A	0.3792	0.3348	G	4.696	0.03023	1.214	46559981	VDR	vitamin D receptor
6	rs6907458	A	0.07772	0.05556	G	4.533	0.03325	1.433	32279266	Chr6 Mapping	Notch 4
4	rs2227306	A	0.364	0.4087	G	4.532	0.03327	0.8279	74972090	IL8	interleukin 8
12	rs11053624	G	0.07143	0.0969	A	4.307	0.03795	0.7169	10174978	CLEC7A (Dectin)	dendritic cell-associated C-type lectin 1
22	rs721930	G	0.2318	0.1971	C	3.935	0.0473	1.229	15960362	IL17R	interleukin 17 receptor
6	rs9296012	A	0.2021	0.1696	G	3.875	0.04902	1.24	32303310	Chr6 Mapping	Notch 4
4	rs11730667	G	0.4054	0.447	A	3.797	0.05134	0.8438	74965246	IL8	
22	rs2041629	A	0.1995	0.168	G	3.686	0.05487	1.234	15931698	IL17R	
12	rs2238136	A	0.2358	0.2718	G	3.65	0.05605	0.8264	46563980	VDR	
4	rs2227307	C	0.3964	0.4369	A	3.645	0.05624	0.8462	74971704	IL8	
14	rs178633	C	0.03368	0.02099	G	3.602	0.05771	1.625	22907989	Chr14 Mapping	
14	rs6572754	A	0.2085	0.2428	G	3.558	0.05926	0.8217	22327900	Chr14 Mapping	
6	rs7747909	A	0.2565	0.2223	G	3.531	0.06022	1.206	52162208	IL17	
6	rs9267845	T	0.4547	0.4147	A	3.526	0.06042	1.177	32301676	Chr6 Mapping	
21	rs2284553	A	0.3536	0.3926	G	3.48	0.06212	0.8465	33698565	IFNGR2	
22	rs2241049	G	0.386	0.3476	A	3.473	0.06238	1.18	15962234	IL17R	
4	rs4694637	G	0.4016	0.4408	A	3.392	0.0655	0.8514	74977869	IL8	
6	rs9267853	A	0.2448	0.2799	G	3.377	0.06613	0.8342	32303229	Chr6 Mapping	
22	rs9606603	A	0.4896	0.4508	T	3.287	0.06983	1.169	15936067	IL17R	

FIG. 15B

4	rs4694178	C	0.4016	0.4392	A	3.137	0.07652	0.8567	74977723	IL8
19	rs2277984	A	0.4663	0.5039	G	3.052	0.08062	0.8604	6630511	TNFSF14 (LIGHT)
14	rs12891812	C	0.101	0.1249	A	2.957	0.08548	0.7877	23417976	Chr14 Mapping
4	rs1609798	A	0.274	0.3078	G	2.939	0.08648	0.8489	103894643	NFKB1
1	rs11804284	A	0.09326	0.116	G	2.881	0.08963	0.7837	67411275	IL23R
6	rs10484879	A	0.2526	0.2221	C	2.831	0.09249	1.184	52159916	IL17
6	rs3134798	G	0.1802	0.2091	A	2.812	0.09358	0.8311	32292683	Chr6 Mapping
19	rs379527	C	0.387	0.3523	A	2.811	0.09359	1.161	6627442	TNFSF14 (LIGHT)

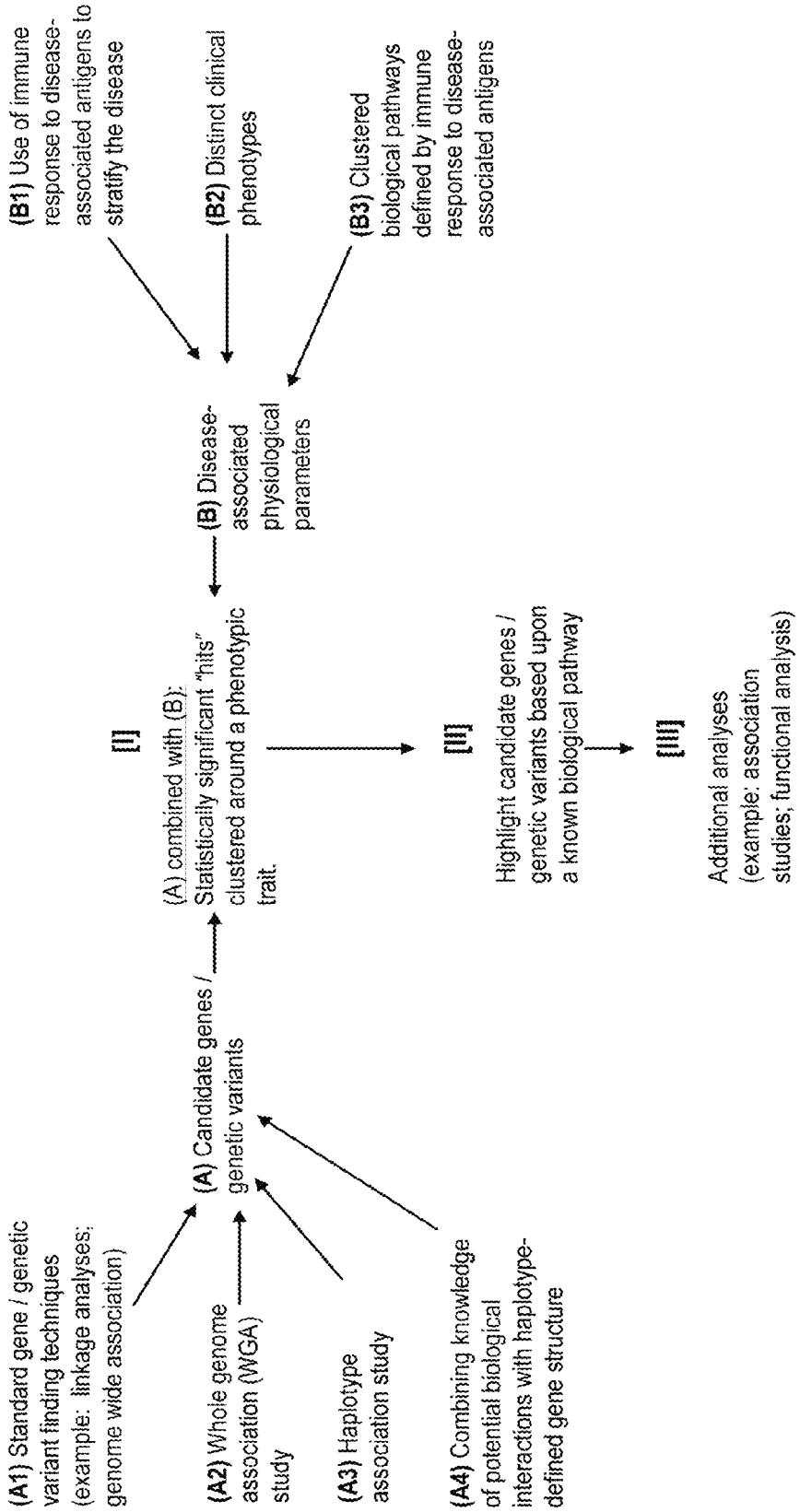
FIG. 16A

CHR	SNP	A1	F_A	F_U	A2	CHISQ	P	OR	Location	Gene Name	Comments
1	rs1569922	A	0.2897	0.3636	G	11.75	0.0006078	0.7138	67376984	IL23R	Interleukin 23 receptor
14	rs2231810	A	0.1659	0.1158	G	9.873	0.001677	1.518	22896659	EFS	Embryonal Fyn-associated substrate isoform 1
14	rs2231805	A	0.1606	0.1118	G	8.997	0.002704	1.52	22899004	EFS	Embryonal Fyn-associated substrate isoform 1
14	rs1951731	G	0.1808	0.1314	A	8.866	0.002905	1.459	23433381	Chr14 Mapping	C14orf165
14	rs1958300	T	0.3806	0.3241	A	6.656	0.009883	1.281	23400032	Chr14 Mapping	Unknown gene
14	rs7148564	A	0.1964	0.1532	T	6.205	0.01274	1.352	22893753	Chr14 Mapping	Unknown gene
19	rs1799969	A	0.05915	0.08911	G	6.14	0.01322	0.6427	10255792	ICAM1	Intercellular adhesion molecule 1
4	rs1609798	A	0.2652	0.3165	G	6.012	0.01421	0.7794	103894643	NFKB1	Nuclear factor kappa-B, subunit 1
1	rs11209008	A	0.01674	0.03261	G	4.879	0.02718	0.5051	67335319	IL23R	Interleukin 23 receptor
14	rs10130976	A	0.03906	0.02183	T	4.853	0.0276	1.822	22474546	Chr14 Mapping	Unknown gene
14	rs10149449	G	0.115	0.08498	A	4.785	0.02871	1.399	22910351	Chr14 Mapping	Interleukin 25
10	rs1399180	A	0.1293	0.164	G	4.51	0.0337	0.7566	8138725	GATA3	GATA binding protein 3 isoform 1
19	rs2234182	A	0.3534	0.4004	G	4.402	0.0359	0.8185	6486080	TNFSF9	tumor necrosis factor ligand 9
4	rs3774965	C	0.02135	0.0377	A	4.338	0.03728	0.5568	103882128	NFKB1	Nuclear factor kappa-B, subunit 1
10	rs1244186	A	0.2221	0.2628	G	4.281	0.03854	0.8007	8132689	GATA3	GATA binding protein 3 isoform 1
6	rs10484879	A	0.2556	0.2154	C	4.274	0.0387	1.25	52159916	IL17	Interleukin 17
19	rs375947	G	0.3135	0.3581	A	4.217	0.04003	0.8184	18041451	IL12RB1	Interleukin 12 receptor beta subunit isoform 1
1	rs2229579	A	0.1272	0.09802	G	4.082	0.04335	1.341	23946468	CNR2	Cannabinoid receptor 2 (macrophage)
6	rs9296012	A	0.2109	0.1749	G	3.981	0.04602	1.261	32303310	Chr6 Mapping	Notch 4
1	rs1004819	A	0.4141	0.3696	G	3.954	0.04677	1.205	67382234	IL23R	Interleukin 23 receptor
4	rs3774968	A	0.4764	0.4315	G	3.839	0.05008	1.199	103888305	NFKB1	
14	rs11160711	A	0.4107	0.3681	G	3.635	0.05658	1.197	19983836	Chr14 Mapping	
14	rs755777	G	0.173	0.1413	A	3.621	0.05707	1.271	20016772	Chr14 Mapping	
12	rs1001449	A	0.01451	0.02668	G	3.43	0.06403	0.5371	10156362	CLEC7A (Dectin)	
19	rs2277984	A	0.4665	0.5089	G	3.415	0.0646	0.8439	6630511	TNFSF14 (LIGHT)	
6	rs7747909	A	0.2556	0.2198	G	3.365	0.06661	1.219	52162208	IL17	
10	rs528778	A	0.1652	0.1976	G	3.356	0.06697	0.8033	8152149	GATA3	

FIG. 16B

19	rs379527	C	0.3789	0.3389	A	3.3	0.06926	1.19	6627442	TNFSF14 (LIGHT)	
1	rs1343151	A	0.2567	0.2935	G	3.216	0.07292	0.8314	67431150	IL23R	
1	rs16828926	A	0.1741	0.1443	G	3.176	0.07473	1.25	23960436	CNR2	
1	rs2501390	A	0.1763	0.1465	G	3.13	0.07689	1.247	23961102	CNR2	
1	rs2502965	G	0.1763	0.1472	A	2.982	0.0842	1.24	23963582	CNR2	
14	rs12891812	C	0.1016	0.1265	A	2.905	0.08833	0.7807	23417976	Chr14 Mapping	
23	rs3764879	G	0.3379	0.2969	C	2.724	0.09886	1.208	12684354	TLR8	
3	rs2633582	C	0.1004	0.07905	A	2.68	0.1016	1.301	113702030	BTLA	
6	rs4711998	A	0.221	0.253	G	2.681	0.1016	0.8377	52158312	IL17	
4	rs3774932	A	0.4978	0.4603	G	2.655	0.1032	1.162	103781378	NFKB1	
1	rs3138156	G	0.05682	0.07555	A	2.641	0.1041	0.7372	6457696	TNFRSF25 (DR3)	
12	rs12580050	T	0.3599	0.3958	A	2.601	0.1068	0.8581	51586470	KRT8/KRT18	Questionable but WORK
14	rs10143597	A	0.3337	0.2994	C	2.589	0.1076	1.172	22912579	Chr14 Mapping	
3	rs9288953	A	0.2958	0.3297	G	2.541	0.1109	0.8538	113685942	BTLA	
12	rs1544410	A	0.3915	0.4269	G	2.456	0.1171	0.8638	46526102	VDR	
22	rs721930	G	0.2242	0.195	C	2.44	0.1183	1.193	15960362	IL17R	Questionable but WORK
14	rs10137082	A	0.2652	0.2341	G	2.438	0.1185	1.18	22909873	Chr14 Mapping	
3	rs2705534	C	0.1004	0.08004	A	2.426	0.1194	1.283	113691075	BTLA	
1	rs11800462	G	0.05492	0.07256	A	2.418	0.12	0.7427	6458767	TNFRSF25 (DR3)	

FIG. 17


(A1) Standard gene / genetic variant finding techniques (example: linkage analyses; genome wide association)
(A2) Whole genome association (WGA) study
(A3) Haplotype association study
(A4) Combining knowledge of potential biological interactions with haplotype-defined gene structure
(A) Candidate genes / genetic variants
[I]
(A) combined with (B): Statistically significant "hits" clustered around a phenotypic trait.
(B) Disease-associated physiological parameters
(B1) Use of immune response to disease-associated antigens to stratify the disease
(B2) Distinct clinical phenotypes
(B3) Clustered biological pathways defined by immune response to disease-associated antigens
[II]
Highlight candidate genes / genetic variants based upon a known biological pathway
[III]
Additional analyses (example: association studies; functional analysis)

METHODS OF IDENTIFYING THE GENETIC BASIS OF A DISEASE BY A COMBINATORIAL GENOMICS APPROACH, BIOLOGICAL PATHWAY APPROACH, AND SEQUENTIAL APPROACH

The present application claims the benefit of priority under 35 U.S.C. §119(e) of provisional application Ser. No. 60/938,796, filed May 18, 2007, and of provisional application Ser. No. 60/939,568, filed May 22, 2007, both of which contents are hereby incorporated by reference.

FIELD OF THE INVENTION

The invention relates generally to the fields of medicine and genetics.

BACKGROUND

All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

Advances in genetics and medicine has led to the understanding that most diseases have a genetic component. For example, variants in the sequence of DNA in an individual may impact a disease by producing variants in the proteins encoded. These encoded proteins; in turn, may perform biological functions that will become altered by the genetic variants. Furthermore, it has become understood that complex diseases often result from the interactions of several genes or their products, each with varying patterns of mutations. By understanding the underlying genetics of a disease or condition, one may find therapeutic targets or opportunities for diagnostics, variants that act as potential susceptibility or protective markers of a disease, or pathways for further research. Thus, there is an enormous need in the art to identify genes, genetic variants and biological pathways that are associated with a disease or condition.

SUMMARY OF THE INVENTION

Various embodiments provide methods of identifying a gene and/or genetic variant involved in the pathogenesis of a disease, the method comprising the steps of performing a genetic association study of a plurality of subjects clinically diagnosed with the disease, using an immune response to an antigen to stratify the disease into one or more subdivisions, and identifying the gene and/or genetic variant involved in the pathogenesis of the disease by clustering statistically significant genetic markers around one or more subdivisions of the disease. In another embodiment, the disease is inflammatory bowel disease. In another embodiment, the genetic association study comprises a whole genome association study. In another embodiment, the genetic association study comprises the use of a haplotype-defined gene structure. In another embodiment, the genetic association study comprises the use of high throughput screening. In another embodiment, the immune response comprises Ab-ASCA, Ab-Cbir1, Ab-I2, Ab-OmpC and/or Ab-pANCA.

Other embodiments provide methods of identifying a biological pathway involved in the pathogenesis of a disease, comprising utilizing an immune expression profile as a quantitative trait to scan the genome of an individual to identify one or more candidate genes, and identifying the biological pathway based upon the presence of one or more candidate genes. In another embodiment, the disease is inflammatory bowel disease. In another embodiment, the immune expression profile comprise the use of Ab-ASCA, Ab-Cbir1, Ab-I2, Ab-OmpC and/or Ab-pANCA.

Other embodiments provide methods of treating a disease, comprising using a combinatorial genomics approach to identify genes, genetic variants and/or biological pathways associated with the disease, and treating the disease. In another embodiment, the disease is inflammatory bowel disease.

Various other embodiments provide methods of treating a disease, comprising using a biological pathway approach to identify genes, genetic variants and/or biological pathways associated with the disease, and treating the disease. In another embodiment, the disease is inflammatory bowel disease.

Other embodiments provide methods of treating a disease, comprising using a sequential approach to identify genes, genetic variants and/or biological pathways associated with the disease, and treating the disease. In another embodiment, the disease is inflammatory bowel disease.

Other embodiments provide methods for discovering the mechanism of a disease, comprising clustering statistically significant genetic markers around a subclinical phenotypic trait, identifying an associated biological pathway, and discovering the mechanism of the disease based upon the associated biological pathway identified.

Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, various embodiments of the invention.

BRIEF DESCRIPTION OF THE FIGURES

Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

FIG. **1** (prior art) depicts an example of how knowledge of potential biologic interactions can be combined with haplotype-defined gene structure. (a) a diagram of the pathogenesis of Crohn's. Disease; (b) a chart of an example of haplotype defined gene interactions.

FIG. **2** (prior art) depicts a diagram demonstrating how genes can alter the immune response to different environmental organisms.

FIG. **3** (prior art) depicts a diagram demonstrating an example of how a clinical phenotype may be the result of bacteria and immune balance in the pathogenesis of a disease.

FIG. **4** (prior art) depicts an example of antigens known to be associated with a disease.

FIG. **5** (prior art) depicts an example of results of independent associations of antibodies, genetic variants, and disease phenotypes (multiple logistic regression). The two associations in the UC-like column are negative associations, while the other columns are positive associations.

FIG. **6** (prior art) depicts a chart as an example of how after whole genome analysis identifies gene variants in a given individual, bioinformatics link gene variants into pathways. The figure depicts integrated pathways discovery clustering of genetic variants by antibody response.

FIG. **7** (prior art) depicts an example related to the protein tyrosine phosphatase receptor family. Each is in a different specific cell type and pathogenetically-associated process.

FIG. **8** (prior art) depicts a diagram depicting an example of combinations of antibodies. The figure describes qualitative responses to multiple microbial antigens.

FIG. **9** (prior art) depicts a graph as an example, demonstrating how quantitative response can be represented by quartiles for each microbial antigen.

FIGS. **10**A-**10**T depict examples of results generated by the Sequential Approach (Combinatorial Genomics Approach followed by Biological Pathway Approach). The figures list a chart of statistically significant associations, organized by columns describing chromosome, position, dbsnp 126, SNP, importance, p-value by permutation test, antibodies, measurement, transformation, gene ID, gene, and gene description.

FIGS. **11**A-**11**B depict examples of results generated by the Sequential Approach. The figures list statistically significant associations of IGA ASCA with corresponding genetic variants.

FIGS. **12**A-**12**B depict examples of results generated by the Sequential Approach. The figures list statistically significant associations of IGG ASCA with corresponding genetic variants.

FIGS. **13**A-**13**B depict examples of results generated by the Sequential Approach. The figures list statistically significant associations of OMPC with corresponding genetic variants.

FIG. **14** depicts examples of results generated by the Sequential Approach. This figure lists statistically significant associations of I2 with corresponding genetic variants.

FIGS. **15**A-**15**B depict examples of results generated by the Sequential Approach. The figures list statistically significant associations of ASCA with corresponding genetic variants.

FIGS. **16**A-**16**B depict examples of results generated by the Sequential Approach. The figures list statistically significant associations of anti-Cbir1 flagellin with corresponding genetic variants.

FIG. **17** depicts a flow chart of an example of the Sequential Approach, where the Combinatorial Genomics Approach (I) is followed sequentially by the Biological Pathway Approach (II, III).

DESCRIPTION OF THE INVENTION

All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton et al., *Dictionary of Microbiology and Molecular Biology* 3rd *ed.*, J. Wiley & Sons (New York, N.Y. 2001); March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure* 5th *ed.*, J. Wiley & Sons (New York, N.Y. 2001); and Sambrook and Russel, *Molecular Cloning: A Laboratory Manual* 3rd *ed.*, Cold Spring Harbor Laboratory Press (Cold Spring Harbor, N.Y. 2001), provide one skilled in the art with a general guide to many of the terms used in the present application.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described.

"Haplotype" as used herein refers to a set of single nucleotide polymorphisms (SNPs) on a gene or chromatid that are statistically associated.

"Protective" and "protection" as used herein refer to a decrease in susceptibility to a disease, including but not limited to CD and UC.

"Odds ratio" as used herein refers to the probability of having a disease if one has the gene, as compared to one who does not have the gene.

"Population attributable risk" as used herein refers to the proportion of the total disease risk due to the particular gene.

As used herein, the term "biological sample" means any biological material from which nucleic acid molecules can be prepared. As non-limiting examples, the term material encompasses whole blood, plasma, saliva, cheek swab, or other bodily fluid or tissue that contains nucleic acid.

Combinatorial Genomics Approach

As disclosed herein, the inventors utilized disease-associated physicological parameters (FIG. **17**, (B)), both individual and combined, as quantitative traits to scan the entire genome in an attempt to focus in on regions where informative genes might be discovered. Alternatively, the quantitative traits may also be used in conjunction with one or more candidate genes/genetic variants (FIG. **17**, (A)). The quantitative traits are utilized to create a specific subcategory of a disease, as opposed to current techniques, which rely on targets that emerge from studies of the disease as a whole. This approach has yielded statistically significant hits across the whole genome in genes and areas that would not have previously been thought relevant, yet clearly are relevant after additional bioinformatics and biologic analyses. The statistically significant hits are thus clustered around a subclinical phenotypic trait and suggest a pathway that can be further explored.

In one embodiment, the present invention provides methods of identifying genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease comprising the following steps: whole genome association study of subjects clinically diagnosed with a disease (FIG. **17**, A**2**); haplotype association study of subjects clinically diagnosed with inflammatory bowel disease (FIG. **17**, A**3**); combine data of potential biological interactions with haplotype-defined gene structure (FIG. **17**, A**4**); use of immune response to disease-associated antigens to stratify the disease (FIG. **17**, B**1**); clustering biological pathways in individuals defined by immune response to disease-associated antigens (FIG. **17**, B**3**).

In another embodiment, the disease-associated physicological parameters (FIG. **17**, (B)) are distinct clinical phenotypes (FIG. **17**, B**2**). In another embodiment, the whole genome association study (FIG. **17**, A**2**) uses known genetic markers. In another embodiment, the whole genome association study (FIG. **17**, A**2**) uses SNPs. In another embodiment, the whole genome association study (FIG. **17**, A**2**) describes biological and/or statistical interactions between genes. In another embodiment, the haplotype association study (FIG. **17**, A**3**) captures the true extent of the Population Attributable Risk. In another embodiment, the haplotype association study (FIG. **17**, A**3**) provides rapid identification of high-impact subjects to be sequenced.

In another embodiment, the identification of genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease, provide methods of identifying biological pathways that, either alone or in combination, are important to the pathogenesis of the disease.

In another embodiment, the identification of genes and genetic variants that either alone or in combination, are important to the pathogenesis of a disease, provide methods of identifying biological pathways that, either alone or in combination, are important to the pathogenesis of an alternative disease. In another embodiment, the identification of genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease, provide methods of identifying additional genes and genetic variants that, either alone or in combination, are important to the pathogenesis of the disease. In another embodiment, the identification of genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease, provide methods of identifying additional genes and genetic variants that, either alone or in combination, are important to the pathogenesis of an alternative disease. In another embodiment, the identification of the genes and/or genetic variants allow functional analysis specific to an individual being treated. In another embodiment, the functional analysis allows a targeted and effective treatment for the individual, where the individual is treated by inhibiting or enhancing the products of the genes and/or genetic variants.

In another embodiment, the present invention provides methods of treatment of a disease in an individual by the following steps: determine the presence of integrated pathogenic pathways in the individual; diagnose the individual for a disease subtype; administer therapy combinations specific to the individual's disease diagnosis. In another embodiment, the present invention provides methods of treatment of a disease in an individual by the following steps: determine the presence of integrated pathogenic pathways in the individual; diagnose the individual for a disease subtype; target integrated pathogenic pathways for inhibition.

In one embodiment, the present invention provides a kit that includes at least one of the following: genetic markers, haplotypes, and antibodies. In another embodiment, the kit includes antibodies to stratify the disease.

In one embodiment, the present invention provides methods of diagnosing susceptibility to a disease by determining the presence or absence of immune responses to antigen. In another embodiment, the present invention provides methods of diagnosing susceptibility to a specific subtype of a disease by determining the presence or absence of immune responses to antigen.

In another embodiment, the present invention provides methods of prognosis of a disease by determining the presence or absence of immune responses to antigen. In another embodiment, the present invention provides methods of treatment of a disease by inhibiting expression of immune responses to antigen.

In another embodiment, the present invention provides methods to vaccinate an individual in need thereof against a disease, by administering a composition that includes antigen to disease-associated antibodies. In another embodiment, the antigen to disease-associated antibodies modulate innate immunity in the individual.

In another embodiment, the present invention provides methods of diagnosing susceptibility to a disease in an individual by identifying genes and genetic variants that, either alone or in combination, are important to the pathogenesis of the disease. In another embodiment, the present invention provides methods of prognosis of a disease in an individual by identifying genes and genetic variants that, either alone or in combination, are important to the pathogenesis of the disease. In another embodiment, the present invention provides methods of treatment of a disease in an individual by inhibiting identified genes and genetic variants that, either alone or in combination, are important to the pathogenesis of the disease.

In one embodiment, the present invention provides methods of providing functional constructs of genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease comprising the following steps: identify genes and genetic variants that, while not apparent as associated with a subclinical phenotypic trait as a whole, are associated with specific antibodies of the subclinical phenotypic trait. In another embodiment, the functional construct of genes and genetic variants provide identification of additional genes and genetic variants that, either alone or in combination, are important to the pathogenesis of the disease.

Biological Pathway Approach

As disclosed herein, the inventors highlighted candidate genes/genetic variants based upon a known biological pathway (FIG. **17**, II), but whose role in a disease and/or disorder had not yet been identified prior, to scan DNA samples of a case-control cohort. Candidate genes are thus interrogated in combination. From the group of highlighted candidate genes/genetic variants (FIG. **17**, II), additional analyses (FIG. **17**, III) are utilized to narrow relevant genes further.

In one embodiment, the present invention provides methods of identifying genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease comprising the following steps: highlighting candidate genes/genetic variants based upon a known biological pathway (FIG. **17**, II); additional analyses to narrow the relevant genes further (FIG. **17**, III). In another embodiment, the genetic variants are SNPs and/or haplotypes. In another embodiment, the additional analyses is functional analysis, association studies and/or standard genetic techniques.

In another embodiment, the identification of genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease, provide methods of identifying targets for treatment and/or therapy. In another embodiment, the present invention provides methods of treatment of a disease by inhibiting the product of genes and genetic variants that have been identified as, either alone or in combination, important to the pathogenesis of the disease. In another embodiment, the present invention provides methods of treatment of a disease by enhancing the product of genes and genetic variants that have been identified as, either alone or in combination, important for protection against the pathogenesis of the disease.

In one embodiment, the present invention provides methods of identifying additional pathways that, either alone or in combination, are important to the pathogenesis of a disease comprising the following steps: selecting. SNPs for genes related to a pathway possibly involved with a disease; genotyping SNPs in a disease case-control cohort; establishing haplotypes from SNPs genotyped; test for association of SNPs with disease; utilizing associated SNPs, test for association of additional genes and genetic variants in a related pathway.

In one embodiment, the present invention provides a kit that includes at least one of: SNPs, haplotypes, and genotyping assays.

In another embodiment, the present invention provides methods of diagnosing susceptibility for a disease in an individual by identifying genes and genetic variants in the individual that, either alone or in combination, are important to the pathogenesis of the disease. In another embodiment, the present invention provides methods of prognosis of a disease in an individual by identifying genes and genetic variants that,

either alone or in combination, are important to the pathogenesis of the disease. In another embodiment, the present invention provides methods of treatment of a disease in an individual by inhibiting the product of genes and genetic variants that, either alone or in combination, are important to the pathogenesis of the disease. In another embodiment, the present invention provides methods of treatment of disease in an individual by enhancing the product of genes and genetic variants that, either alone or in combination, are important for protection against the pathogenesis of the disease.

Sequential Approach

Combinatorial Genomics Approach followed by Biological Pathway Approach

As disclosed herein, the inventors utilized a Sequential Approach whereby the Biological Pathway Approach is used as an extension of the Combinatorial Genomics Approach. In the Sequential Approach, inventors utilize disease-associated physiological parameters (FIG. **17**, B), both individual and combined, as quantitative traits to scan the entire genome in an attempt to focus in on regions where informative genes might be discovered. The statistically significant hits are thus clustered around a phenotypic trait (FIG. **17**, I) and suggest a pathway that can be further explored with the Biological Pathway Approach. Candidate genes are then interrogated in combination, highlighted based upon a known biological pathway that is possibly involved in the disease and/or disorder (FIG. **17**, II), and may undergo additional analyses (FIG. **17**, III) to identify additional biological pathways, genes and/or genetic variants.

In one embodiment, the present invention provides methods of identifying genes and genetic variants that, either alone or in combination, are important to the pathogenesis of a disease comprising the following steps: cluster statistically significant hits around a phenotypic trait (FIG. **17**, I), highlighting candidate genes/genetic variants based upon a known biological pathway (FIG. **17**, II), followed sequentially by additional analyses (FIG. **17**, III).

Variety of Methods and Materials

A variety of methods can be used to determine the presence or absence of a variant allele or haplotype. As an example, enzymatic amplification of nucleic acid from an individual may be used to obtain nucleic acid for subsequent analysis. The presence or absence of a variant allele or haplotype may also be determined directly from the individual's nucleic acid without enzymatic amplification.

Analysis of the nucleic acid from an individual, whether amplified or not, may be performed using any of various techniques. Useful techniques include, without limitation, polymerase chain reaction based analysis, sequence analysis and electrophoretic analysis. As used herein, the term "nucleic acid" means a polynucleotide such as a single or double-stranded DNA or RNA molecule including, for example, genomic DNA, cDNA and mRNA. The term nucleic acid encompasses nucleic acid molecules of both natural and synthetic origin as well as molecules of linear, circular or branched configuration representing either the sense or antisense strand, or both, of a native nucleic acid molecule.

The presence or absence of a variant allele or haplotype may involve amplification of an individual's nucleic acid by the polymerase chain reaction. Use of the polymerase chain reaction for the amplification of nucleic acids is well known in the art (see, for example, Mullis et al. (Eds.), The Polymerase Chain Reaction, Birkhauser, Boston, (1994)).

A TaqmanB allelic discrimination assay available from Applied Biosystems may be useful for determining the presence or absence of, simply by way of example, a TL1A variant allele. As will be readily appreciated by those of skill in the art, numerous other genes, variant alleles and/or haplotypes can be studied in this fashion. In a TaqmanB allelic discrimination assay, a specific, fluorescent, dye-labeled probe for each allele is constructed. The probes contain different fluorescent reporter dyes such as FAM and VICTM to differentiate the amplification of each allele. In addition, each probe has a quencher dye at one end which quenches fluorescence by fluorescence resonant energy transfer (FRET). During PCR, each probe anneals specifically to complementary sequences in the nucleic acid from the individual. The 5' nuclease activity of Taq polymerase is used to cleave only probe that hybridize to the allele. Cleavage separates the reporter dye from the quencher dye, resulting in increased fluorescence by the reporter dye. Thus, the fluorescence signal generated by PCR amplification indicates which alleles are present in the sample. Mismatches between a probe and allele reduce the efficiency of both probe hybridization and cleavage by Taq polymerase, resulting in little to no fluorescent signal. Improved specificity in allelic discrimination assays can be achieved by conjugating a DNA minor grove binder (MGB) group to a DNA probe as described, for example, in Kutyavin et al., "3'-minor groove binder-DNA probes increase sequence specificity at PCR extension temperature, "Nucleic Acids Research 28:655-661 (2000)). Minor grove binders include, but are not limited to, compounds such as dihydrocyclopyrroloindole tripeptide (DPI).

Sequence analysis also may also be useful for determining the presence or absence of a variant allele or haplotype. As will be readily appreciated by those of skill in the art, numerous other genes, variant alleles and/or haplotypes can be studied in this fashion.

Restriction fragment length polymorphism (RFLP) analysis may also be useful for determining the presence or absence of a particular allele (Jarcho et al. in Dracopoli et al., Current Protocols in Human Genetics pages 2.7.1-2.7.5, John Wiley & Sons, New York; Innis et al., (Ed.), PCR Protocols, San Diego: Academic Press, Inc. (1990)). As used herein, restriction fragment length polymorphism analysis is any method for distinguishing genetic polymorphisms using a restriction enzyme, which is an endonuclease that catalyzes the degradation of nucleic acid and recognizes a specific base sequence, generally a palindrome or inverted repeat. One skilled in the art understands that the use of RFLP analysis depends upon an enzyme that can differentiate two alleles at a polymorphic site.

Allele-specific oligonucleotide hybridization may also be used to detect a disease-predisposing allele. Allele-specific oligonucleotide hybridization is based on the use of a labeled oligonucleotide probe having a sequence perfectly complementary, for example, to the sequence encompassing a disease-predisposing allele. Under appropriate conditions, the allele-specific probe hybridizes to a nucleic acid containing the disease-predisposing allele but does not hybridize to the one or more other alleles, which have one or more nucleotide mismatches as compared to the probe. If desired, a second allele-specific oligonucleotide probe that matches an alternate allele also can be used. Similarly, the technique of allele-specific oligonucleotide amplification can be used to selectively amplify, for example, a disease-predisposing allele by using an allele-specific oligonucleotide primer that is perfectly complementary to the nucleotide sequence of the dis-

ease-predisposing allele but which has one or more mismatches as compared to other alleles (Mullis et al., supra, (1994)). One skilled in the art understands that the one or more nucleotide mismatches that distinguish between the disease-predisposing allele and one or more other alleles are preferably located in the center of an allele-specific oligonucleotide primer to be used in allele-specific oligonucleotide hybridization. In contrast, an allele-specific oligonucleotide primer to be used in PCR amplification preferably contains the one or more nucleotide mismatches that distinguish between the disease-associated and other alleles at the 3' end of the primer.

A heteroduplex mobility assay (HMA) is another well known assay that may be used to detect a SNP or a haplotype. HMA is useful for detecting the presence of a polymorphic sequence since a DNA duplex carrying a mismatch has reduced mobility in a polyacrylamide gel compared to the mobility of a perfectly base-paired duplex (Detwart et al., Science 262:1257-1261 (1993); White et al., Genomics 12:301-306 (1992)).

The technique of single strand conformational, polymorphism (SSCP) also may be used to detect the presence or absence of a SNP and/or a haplotype (see Hayashi, K., Methods Applic. 1:34-38 (1991)). This technique can be used to detect mutations based on differences in the secondary structure of single-strand DNA that produce an altered electrophoretic mobility upon non-denaturing gel electrophoresis. Polymorphic fragments are detected by comparison of the electrophoretic pattern of the test fragment to corresponding standard fragments containing known alleles.

Denaturing gradient gel electrophoresis (DGGE) also may be used to detect a SNP and/or a haplotype. In DGGE, double-stranded DNA is electrophoresed in a gel containing an increasing concentration of denaturant; double-stranded fragments made up of mismatched alleles have segments that melt more rapidly, causing such fragments to migrate differently as compared to perfectly complementary sequences (Sheffield et al., "Identifying DNA Polymorphisms by Denaturing Gradient Gel Electrophoresis" in Innis et al., supra, 1990).

Other molecular methods useful for determining the presence or absence of a SNP and/or a haplotype are known in the art and useful in the methods of the invention. Other well-known approaches for determining the presence or absence of a SNP and/or a haplotype include automated sequencing and RNAase mismatch techniques (Winter et al., Proc. Natl. Acad. Sci. 82:7575-7579 (1985)). Furthermore, one skilled in the art understands that, where the presence or absence of multiple alleles or haplotype(s) is to be determined, individual alleles can be detected by any combination of molecular methods. See, in general, Birren et al. (Eds.) Genome Analysis: A Laboratory Manual Volume 1 (Analyzing DNA) New York, Cold Spring Harbor Laboratory Press (1997). In addition, one skilled in the art understands that multiple alleles can be detected in individual reactions or in a single reaction (a "multiplex" assay). In view of the above, one skilled in the art realizes that the methods of the present invention for diagnosing or predicting susceptibility to or protection against CD, UC or other diseases in an individual may be practiced using one or any combination of the well known assays described above or another art-recognized genetic assay.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. For purposes of the present invention, the following terms are defined below.

EXAMPLES

The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Example 1

Combinatorial Genomics Approach Generally

The inventors utilized antibody expression profiles, both individual and combined, as quantitative traits to scan the entire genome to focus in on regions where informative genes might be discovered. The quantitative traits are utilized to create a specific subcategory of a disease, as opposed to current techniques, which rely on targets that emerge from studies of the disease as a whole. This approach has yielded statistically significant hits across the whole genome in genes and areas that would not have previously been thought relevant, yet clearly are relevant after additional bioinformatics and biologic analyses. The statistically significant hits are thus clustered around a subclinical phenotypic trait and suggest a pathway that can be further explored. A particularly inventive feature of the present invention, therefore, involves conducting a whole genome association study of individuals in whom antibodies have already been assessed in the aforementioned manner, so as to suggest particular pathways for exploration.

Example 2

Steps for a Combinatorial Genomics Approach

(1) Conduct whole genome association study of subjects clinically diagnosed with inflammatory bowel disease; (2) Perform haplotype association study of subjects clinically diagnosed with inflammatory bowel disease; (3) Combine knowledge of potential biological interactions with haplotype-defined gene structure; (4) Use of antibodies to antigens to stratify the disease; (5) Use immune responses to discover unique genes; (5) Cluster pathways in individuals defined by immune response to antigens.

Example 3

Biological Pathway Approach

The inventors identified genes and genetic variants that, either alone or in combination, are important to the pathogenesis of inflammatory bowel disease comprising the following steps: (1) selecting TagSNPs for major Caucasian haplotypes in eight genes related to the IL12/IL23 pathway; (2) genotyped in a Crohn's Disease case-control cohort; (3) used to infer haplotypes; (4) and then tested for association with Crohn's Disease.

Example 4

Case-Control Cohort

The inventors recruited subjects at the Cedars-Sinai Medical Center Inflammatory Bowel Disease center under the

approval of the Cedars-Sinai Medical Center Institutional Review Board. Disease phenotype was assigned using a combination of standard endoscopic, histological, and radiographic features. Ashkenazi Jewish ethnicity was assigned when one or more grandparents were of Ashkenazi Jewish origin.

Example 5

Selection of SNPs

SNPs were selected by applying the "Tagger" option in the program Haploview to data from the International HapMap Project. SNPs that "tagged" major Caucasian haplotypes and at the same time that were predicted to be compatible with the Illumina genotyping technology using the Illumina Assay Design Tool were genotyped in the initial phases of the study. Since the inventors were interested in major genetic effects for the study rather than rare alleles, the goal of "tagging" was to find a set of tagSNPs in linkage disequilibrium with all SNPs in the HapMap data with a minor allele frequency≤5%; in some cases this goal was not completely met due to the limitations of the Illumina technology. A few SNPs were also added that were: 1) non-synonymous and had a minor allele frequency greater than 3%, 2) redundant in order to accommodate some assay failure in the initial Illumine run, and 3) markers suggested by information provided by SeattleSNPs. SNPs showing positive associations were selected for further genotyping by ABI technology.

Example 6

Genotyping

DNA was isolated from Epstein Barr virus transformed lymphoblastoid cell lines using proteinase K digestion, organic extraction, and ethanol precipitation. Single nucleotide markers (SNPs) were genotyped using one of two methods: (1) the oligonucleotide ligation assay, Illumine Golden Gate technology, following the manufacturer's protocol (Illumina, San Diego, Calif.), and (2) the 5'-extension reaction, TaqMan MGB technology, following the manufacturer's protocol (Applied Biosystems). Consistency of SNP genotyping between the two methods was checked for each SNP by genotyping 100 samples with both methods.

Example 7

Statistical Analyses

Haplotype blocks were determined using the "Tagger" routine of the program Haploview. Haplotypes of subjects were inferred from the genotyping data using the program PHASE v2. The association of the presence of a haplotype was tested using the chi-square test and the significance of results was assessed by applying a permutation test to the data in order to correct for multiple testing due to the number of haplotypes. Results with significance were defined by $p<0.05$ by permutation test. Due to sample size considerations, the results were for all CD and control subjects with Jewish and non-Jewish subjects combined. The notable exception to this was that an IL17A "risk" haplotype specific to the non-Jewish population was identified in the hypothesis-generating phase of the study and used for subsequent gene-gene interaction studies. Population attributable risk was estimated by assuming that 1) the frequency of a particular haplotype in the controls reflected the population frequency of that haplotype, and 2) the odds ratio for the association of a given haplotype reflected the relative risk of that haplotype for Crohn's disease. Haplotypes were numbered in order of frequency in controls (H1, H2, and so forth) and the nucleotides for each tagSNP listed according to the forward strand of the NCBI human genome build 36 and dbSNP. A "major" haplotype is a haplotype with a population frequency greater than 5% in the controls.

Example 8

TABLE 1

Statistically significant associations, as organized by clusters of Cbirl antibodies and pathway-related clustering of genes.

PATHWAY:	CORRESPONDING GENE:
TCR Activation	TCR alpha
	PRPTC
	NGAT5
Transcription	1KBKAP
	F1B1
	RA17
Endothelial Response	ZF124-VEGF
Myeloid Activation	TLR8

Example 9

TABLE 2

Statistically significant associations, as organized by clusters of 12 antibodies and pathway-related clustering of genes.

PATHWAY:	CORRESPONDING GENE:
Innate Cell Signaling/Channels/GTPase.	KCNMAI (CGD - phenocopy)
	K1D676
	S1PAL2
	SRGAP3
	RHOU
TCR Activation	TCR alpha
	PAK7

Example 10

TABLE 3

Statistically significant associations, as organized by clusters of ASCA antibodies and pathway-related clustering of genes.

PATHWAY:	CORRESPONDING GENE:
Cell Activation/Endosome	EHD3
	SRGAP3
	CDC42 (RAL)
Adherence	PTPRB
TCR Activation	BTNL2
	SAR (MHC-II)
	PAK7
Innate Channel	KCNMA1

Example 11

TABLE 4

Statistically significant associations, as organized by clusters of OmpC antibodies and pathway-related clustering of genes.

PATHWAY:	CORRESPONDING GENE:
Myeloidal Function	PTPRD
NRXN3 Adhesion	NRXN3

Example 12

TABLE 5

Statistically significant associations, as organized by all antibodies (Cbir1, 12, ASCA, OmpC) and pathway-related clustering of genes.

PATHWAY:	CORRESPONDING GENE:
TCR-alpha T cell	
Innate Activation	KCNMA1
Extracellular Matrix	CHSS 11
Transactivation - ZNF780	NBPLD3
Neral - NRXN3	

While the description above refers to particular embodiments of the present invention, it should be readily apparent to people of ordinary skill in the art that a number of modifications may be made without departing from the spirit thereof. The presently disclosed embodiments are, therefore, to be considered in all respects as illustrative and not restrictive. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. Furthermore, one of skill in the art would recognize that the invention can be applied to any number of conditions and disorders and diseases. It will also be readily apparent to one of skill in the art that the invention can be used in conjunction with a variety of phenotypes, such as serological markers, additional genetic variants, biochemical markers, abnormally expressed biological pathways, and variable clinical manifestations.

The invention claimed is:

1. A method for determining whether a gene variant and/or a genetic variant has involvement in the pathogenesis of inflammatory bowel disease (IBD), comprising:

obtaining blood samples from patients clinically diagnosed with IBD;

determining whether the gene variant and/or the genetic variant is present in each blood sample by contacting each blood sample with an allele-specific fluorescent-dye-labeled oligonucleotide probe targeting the gene variant and/or the genetic variant, and detecting whether allele-specific binding occurs between the gene variant and/or the genetic variant and the allele-specific fluorescent-dye-labeled oligonucleotide probe using allele-specific oligonucleotide hybridization assay;

using a *Saccharomyces cerevisiae* antigen to assay each blood sample to detect the presence of an anti-*Saccharomyces cerevisiae* antibody (Ab-ASCA) by detecting an antigen-antibody complex generated through binding between the Ab-ASCA and the *Saccharomyces cerevisiae* antigen;

using a *Pseudomonas fluorescens*-related sequence I2 antigen to assay each blood sample to detect the presence of an antibody to *Pseudomonas fluorescens*-related sequence I2 (Ab-I2) by detecting an antigen-antibody complex generated through binding between the Ab-I2 and the *Pseudomonas fluorescens*-related sequence I2 antigen;

using a *Escherichia coli* outer membrane porin C antigen to assay each blood sample to detect the presence of an antibody to *Escherichia coli* outer membrane porin C (Ab-OmpC) by detecting an antigen-antibody complex generated through binding between the Ab-OmpC and the *Escherichia coli* outer membrane porin C antigen;

using a neutrophil antigen to assay each blood sample to detect the presence of a perinuclear anti-neutrophil cytoplasmic antibody (Ab-pANCA) by detecting an antigen-antibody complex generated through binding between the Ab-pANCA and the neutrophil antigen;

determining each blood sample's immune expression profile based on the presence of Ab-ASCA, Ab-OmpC, Ab-I2 and/or Ab-pANCA;

stratifying IBD into one or more subdivisions based on the immune expression profiles of each blood sample;

performing a genetic association study by associating the presence of the gene variant and/or the genetic variant with the one or more subdivisions of IBD; and

determining the gene variant and/or the genetic variant as having involvement in the pathogenesis of IBD if the presence of the gene variant and/or the genetic variant is statistically significantly clustered around the one or more subdivisions of IBD.

2. The method of claim **1**, wherein IBD is Crohn's disease (CD) or ulcerative colitis (UC).

3. The method of claim **1**, wherein the genetic association study comprises a whole genome association study.

4. The method of claim **1**, wherein the genetic association study comprises the use of a haplotype-defined gene structure.

5. The method of claim **1**, wherein the genetic association study comprises the use of high throughput screening.

6. A method for determining whether a biological pathway has involvement in the pathogenesis of IBD, comprising:

obtaining blood samples from patients clinically diagnosed with IBD;

determining whether a genetic variant in the biological pathway is present in each blood sample by contacting each blood sample with an allele-specific fluorescent-dye-labeled oligonucleotide probe targeting the genetic variant, and detecting whether allele-specific binding occurs between the genetic variant and the allele-specific fluorescent-dye-labeled oligonucleotide probe using allele-specific oligonucleotide hybridization assay;

using a *Saccharomyces cerevisiae* antigen to assay each blood sample to detect the presence of an anti-*Saccharomyces cerevisiae* antibody (Ab-ASCA) by detecting an antigen-antibody complex generated through binding between the Ab-ASCA and the *Saccharomyces cerevisiae* antigen;

using a *Pseudomonas fluorescens*-related sequence I2 antigen to assay each blood sample to detect the presence of an antibody to *Pseudomonas fluorescens*-related sequence I2 (Ab-I2) by detecting an antigen-antibody complex generated through binding between the Ab-I2 and the *Pseudomonas fluorescens*-related sequence I2 antigen;

using a *Escherichia coli* outer membrane porin C antigen to assay each blood sample to detect the presence of an antibody to *Escherichia coli* outer membrane porin C (Ab-OmpC) by detecting an antigen-antibody complex generated through binding between the Ab-OmpC and the *Escherichia coli* outer membrane porin C antigen;

using a neutrophil antigen to assay each blood sample to detect the presence of a perinuclear anti-neutrophil cytoplasmic antibody (Ab-pANCA) by detecting an antigen-antibody complex generated through binding between the Ab-pANCA and the neutrophil antigen;

determining each blood sample's immune expression profile based on the presence of Ab-ASCA, Ab-OmpC, Ab-I2 and/or Ab-pANCA;

stratifying IBD into one or more subdivisions based on the immune expression profiles of each blood sample;

performing a genetic association study by associating the presence of the genetic variant with the one or more subdivisions of IBD; and

determining the biological pathway as having involvement in the pathogenesis of IBD if the presence of the genetic variant is statistically significantly associated with the one or more subdivisions of IBD.

7. The method of claim **6**, wherein IBD is Crohn's disease (CD).

8. The method of claim **6**, wherein IBD is ulcerative colitis (UC).

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